New Developments in Metal-Mediated Heterocycle Synthesis

by

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Dedicated to L.

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Brett Hopkins helped me realize that having children in graduate school is possible. I am only aware of two other PhD organic chemists that had four kids when they obtained their PhDs or completed their postdocs, and I have been uniquely blessed by having mentors that don't let me use family as an excuse for poor work, and also don't judge me or look down upon me for raising a family during graduate school.

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Lastly, I have to thank Lynette for everything. Although I don't remember the conversation, Lynette told me I should just get a job after graduating from GVSU, but I thought I had something to contribute in the field of chemistry. She followed me to the University of Michigan, demonstrating a servant's heart in so many ways. Her work ethic and devotion

to important things inspires me to adopt a better lifestyle. As we go to Atlanta for my postdoctoral training, I am glad I get to continue life with Lynette at my side. I am truly blessed by her.

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List of Acronyms and Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
Ar	generic aryl group
BINOL	1,1’-bis(2-naphthol)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	carbobenzyloxy
CDI	1,1’-carbonyldiimidazole
Cy	cyclohexyl
dba	dibenzylideneacetone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio

esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
Het	generic heterocycle
MPM	*p*-methoxybenzyl
Ms	methane sulfonyl
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *para*-toluenesulfonate
R	general group
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
Tf	triflate
TFA	trifluoroacetic acid
Ts	*p*-toluenesulfonyl
X	general halide

Abstract

This thesis describes the development of new metal-mediated chemical reactions which enable the rapid construction of stereocontrolled heterocycles. The reactions proceed by functionalizing olefins to form a ring, a carbon-heteroatom bond, a carbon-carbon bond or carbon-hydrogen bond, and 1-2 stereocenters with high selectivity. This strategy is especially attractive for generating libraries of new compounds simply by exchanging the coupling partners. Three new methods are described below for the formation of guanidines, sulfamides, and tetrahydrofurans.

Cyclic guanidines are prevalent motifs in a wide array of pharmaceuticals and natural products. In addition, the synthetic community has exhibited a strong interest in utilizing silver as a catalyst for the formation of heterocycles. For these reasons, a new method was developed which accomplishes the silver-catalyzed hydroamination reaction of tosyl-protected guanidines onto unactivated olefins. This intramolecular cyclization reaction proceeds using catalytic amounts of silver (15-20%) in the presence of atmospheric oxygen and one equivalent of strong base. The cyclic guanidines are constructed in high yields (up to 98%). Sterically congested quaternary centers can be formed by cyclization onto 1,1-disubstitued alkenes. Also, bicyclic guanidines are formed in high yields (using 40 mol% $AgNO_3$).

Sulfamides are present in a variety of biologically active compounds and often serve as isosteres for ureas in the medicinal chemist's toolbox. Due to their biological and synthetic importance, an asymmetric synthesis of cyclic sulfamides was developed showcasing the ability of the Pd-catalyzed carboamination reaction for rapidly generating a diverse set of compounds in high yield and enantioselectivity. The new asymmetric method utilized $Pd_2(dba)_3$ and the commercially available chiral ligand (*S*)-Siphos-PE for high enantio-induction. Transformations of electron-neutral or electron-rich aryl bromides provided the highest levels of asymmetric induction whereas use of electron-poor electrophiles resulted in lower selectivity. The presence of water in the reaction had a remarkable influence on yield, improving the yield by up to 45%. The possible influence of competing *syn* and *anti* aminopalladation pathways prompted a mechanistic study by deuterium labeling studies which showed that the predominant mechanistic pathway occurred by *syn* aminopalladation. This asymmetric reaction has also been applied to the synthesis of 6-membered cyclic sulfamides, although geminal substitution is required in the homoallyl backbone for effective cyclization. This carboamination reaction proceeds in good yields and high enantioselectivity (up to 94% yield, up to 96% ee). A Pd-catalyzed desymmetrization reaction which operates under *anti* aminopalladation conditions was also examined. Asymmetric induction is achieved using axially chiral ligands with electron-rich phosphines, and hopefully, further manipulation of the ligand will improve enantioselectivity.

Tetrahydrofurans bearing substituents at the C2 position are prominent motifs present in many biologically active compounds. Early developments in the Wolfe group described the racemic palladium-catalyzed alkoxylation reaction which formed the

heterocyclic ring along with a C–O bond, a C–C bond, and 1-2 stereocenters with high diastereoselectivity. Conversely, a palladium-catalyzed enantioselective alkoxylation reaction remained elusive even though the racemic reaction was described in 2004. The realization of an enantioselective alkoxylation reaction employed a new chiral ligand with a TADDOL backbone. The asymmetric carboalkoxylation reaction proceeds in moderate to good yields (54%-85%) and moderate to good enantiomeric ratios (68:32 to 95:5). High enantioselectivity was obtained for alcohols bearing bulky substituents geminal to the alcohol.

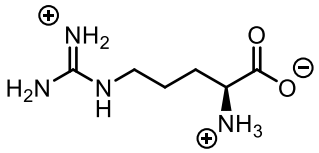
Chapter 1

Application and Synthesis of Cyclic Guanidines

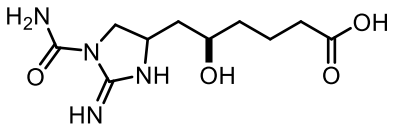
1.1 Background and Significance

Cyclic guanidines are prominent motifs in a variety of natural products and pharmaceuticals as this functional group ultimately derives from the amino acid arginine. In most instances, cyclic guanidines are comprised of 5 or 6-membered rings. **Figure 1.1** showcases a collection of natural products which contain cyclic guanidine motifs.[1] The remarkable feature of cyclic guanidine containing natural products arises from the variety of possible structures derived from different connectivities with the guanidine subunit. For example, batzelladine A[2] bears three differentially functionalized guanidines: a guanidine at the terminus of an aliphatic chain, a guanidine which occupies the periphery of a bicycle, and a third guanidine embedded centrally within a tricyclic core.

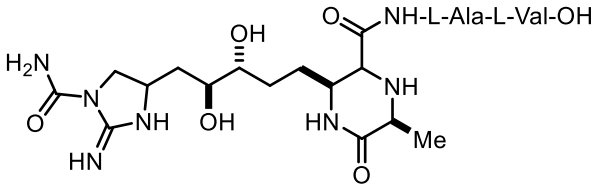
Figure 1.1 Examples of Guanidines in Natural Products



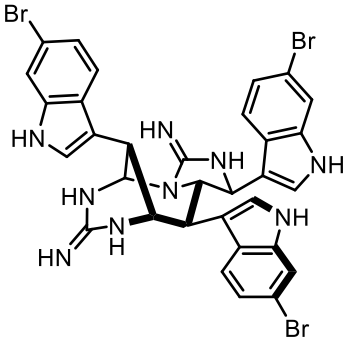
L-Arginine



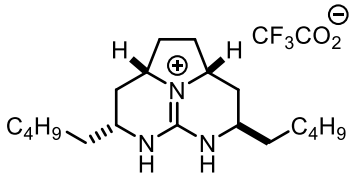
Guadinomic Acid



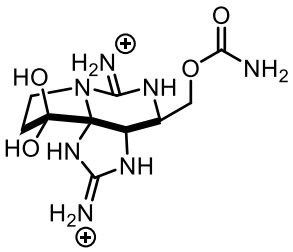
Guadinomines C_2



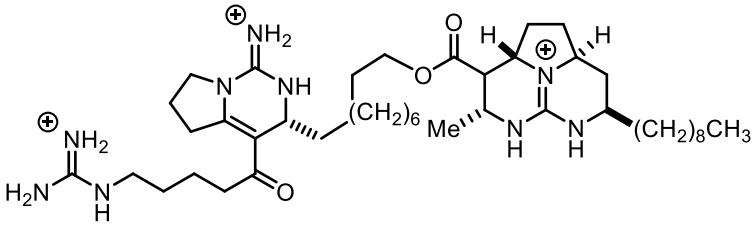
araiosomine C



Merobatzelladine B
Inhibits *Plasmodium falciparum*



(+)-saxitoxin

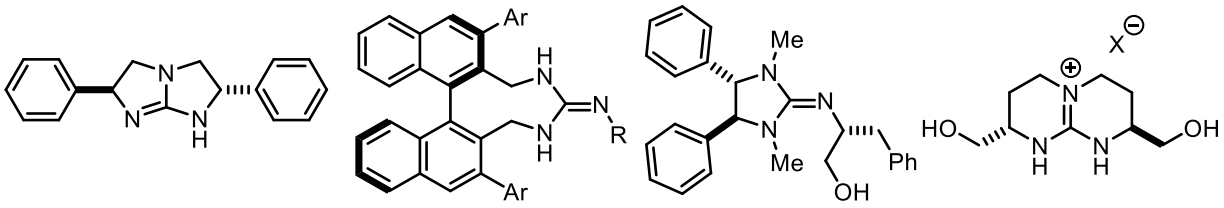


Batzelladine A
HIV gp-120 inhibitor

Due to the unique structural elements in cyclic guanidine natural products and due to the challenge associated with synthesizing these highly polar compounds, the synthetic community has sought the total synthesis of and methods towards many of the natural products outlined in **Figure 1.1**.[1] Besides efforts in total synthesis towards the

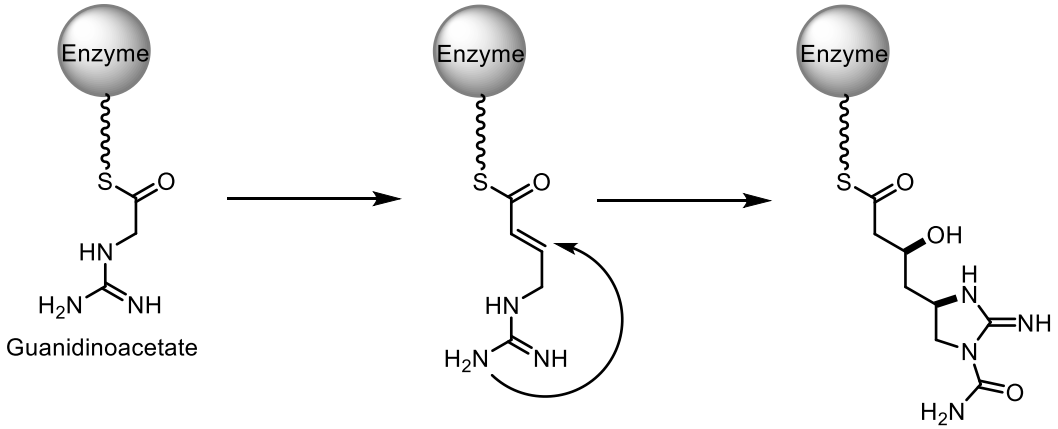
synthesis of cyclic guanidine-containing natural products, cyclic guanidines have found utility in their own right primarily within the realm of organocatalysis.[3]

Figure 1.2 Chiral Cyclic Guanidines as Organocatalysts



Examining the biosynthetic pathway for the guadinomines, which has recently been elucidated, can help understand better how molecular complexity develops towards the formation of cyclic guanidines. This work lends some insight into how Nature accomplishes the formation of cyclic guanidines.[4] Guanidinoacetate is formed by transfer of an amidino group of arginine to the acceptor molecule, the amino acid glycine. Through a series of biochemical reactions, guanidinoacetate is transformed into an α,β-unsaturated diketide that can undergo cyclization with the nucleophilic guanidine to form the heterocycle. The activated electrophile permits ready cyclization of the guanidine. The remarkable ease with which this biosynthetic pathway accomplishes formation of a cyclic guanidine seems to render synthetic efforts towards cyclic guanidines puerile. But, because chemists in general do not have the luxury of enzymes and enzymatic pathways for catalysis, more efficient, sophisticated, and novel methods for C-N bond closure are required which do not always rely on attack of the guanidine onto an activated electrophile.

Figure 1.3 Biosynthetic Pathway for Guadinomines



1.2 Formation of Cyclic Guanidines by Nucleophilic Attack of Acyclic Guanidine Nucleophiles

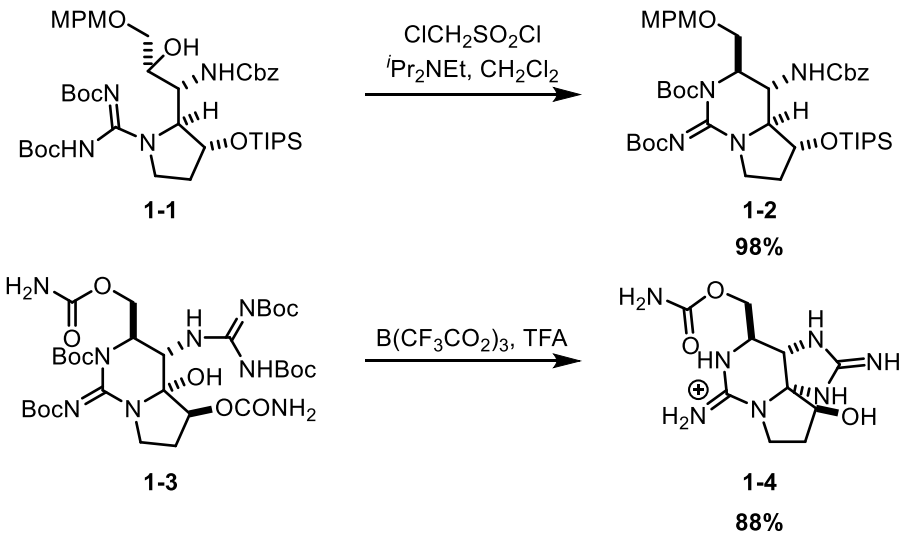
The chemical synthesis of cyclic guanidines has been explored in a wide variety of ways. Natural products containing cyclic guanidine units have garnered the attention of the synthetic community because of the challenge associated with devising syntheses and handling of these compounds. Many cyclic guanidine-containing natural products have been successfully synthesized, and a few highlighted syntheses are described below so that the significance of developing new reactions for generating cyclic guanidines is elucidated. The formation of cyclic guanidines is accomplished by several different strategies depending on the retrosynthetic disconnections associated with the heterocycle (Is the guanidine pre-formed prior to cyclization? Is the guanidine formed in the same instant as the heterocycle? Is the guanidine formed after formation of the hetercycle?).

For the purposes of highlighting the need for the new reaction described in Chapter 2 of this thesis, only reactions which undergo an intramolecular ring-forming event accomplished by a guandine nucleophile for formation of a heterocycle will be

described. In terms of complete synthetic routes mentioned below, please direct your attention to the citation, as each total synthesis is NOT fully described; rather the key step that forms the cyclic guanidine is discussed. By examining the different methods and the different applications of such methods for the formation of cyclic guanidines, the importance of continued development in this area will be highlighted. Also, it is the hope of the author that discussing the methods below will expose the limitations in current existing technology.

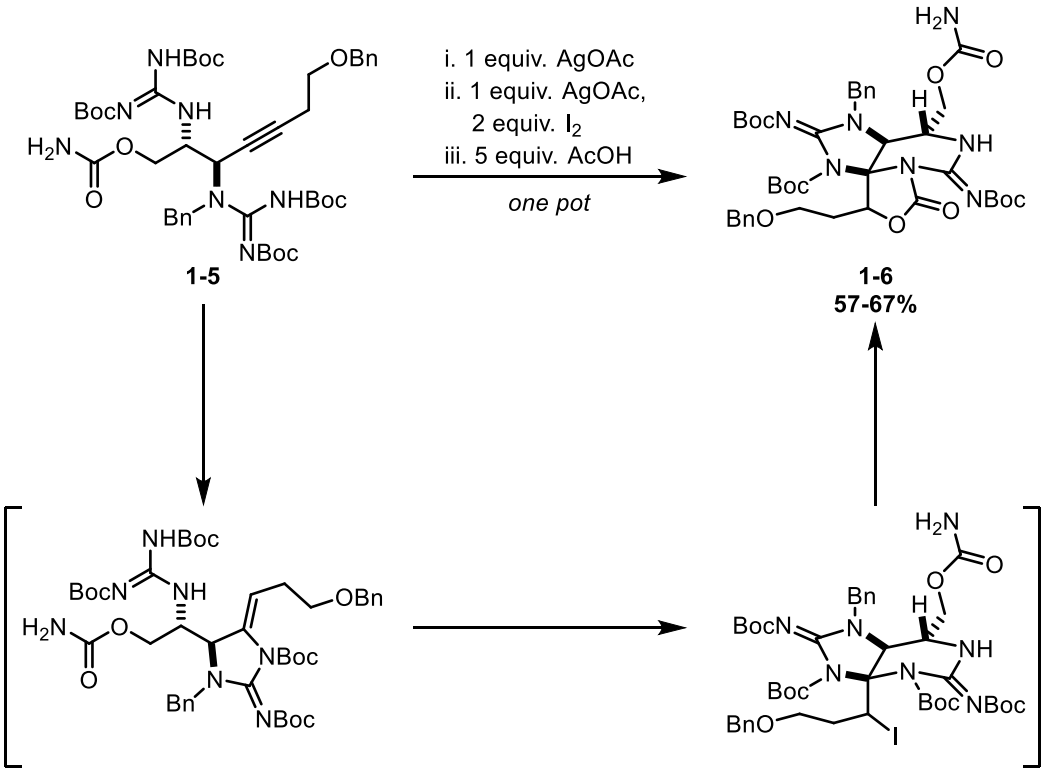
One popular guanidine-containing target for synthetic chemists is saxitoxin (STX) which is a paralytic shellfish toxin utilized as an ion channel probe.[5] STX is comprised of two cyclic guanidines, one of which occupies the boundaries of a bicycle.[6] Numerous groups including Kishi,[7] Jacobi,[8] and Du Bois[9] have developed well-designed synthetic routes towards this natural product, but this body of work will not be described. Instead, this discussion will focus on the work of Nagasawa and Looper which utilize acyclic guanidines as nucleophiles during ring closure events.

Scheme 1.1 Efforts by the Nagasawa Group Towards (+)-Saxitoxin



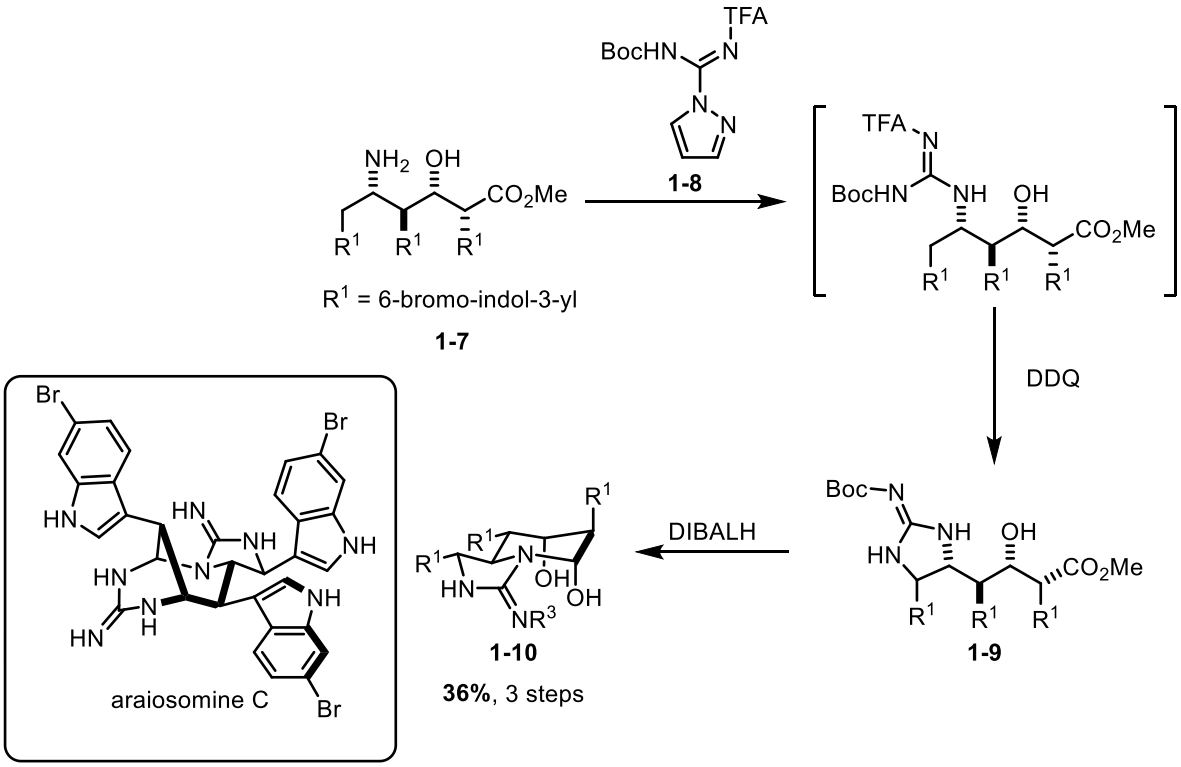
The Nagasawa group capitalized on several unique transformations for realizing the total synthesis of (+)-saxitoxin.[10] In this synthesis, the two cyclic guanidine units were constructed via intramolecular substitution reactions as shown in **Scheme 1.1**. In the first cyclization shown in **Scheme 1.1**, a secondary alcohol is converted into a good leaving group, and subsequent stereospecific S_N2 attack ensues, providing the bicyclic guanidine in great yield (98%). Later in the synthesis, the second cyclic guanidine is formed by interception of an intermediate iminium ion which is formed in the presence of the boron reagent. Further transformations lead to (+)-saxitoxin.

Scheme 1.2 Sequential Cyclizations towards (+)-Saxitoxin



Bhonde and Looper demonstrated a concise stereoselective synthesis of (+)-saxitoxin by implementing a silver(I)-initiated hydroamination cascade which develops the bicyclic guanidinium core.[11] The synthesis was completed in 14 steps from *N*-Boc-L-serine methyl ester. As shown in **Scheme 1.2**, the key tricyclic scaffold was synthesized in one pot by an intramolecular silver-mediated cascade reaction. During this cascade, silver acetate facilitates the hydroamination of the tethered alkyne. Then, iodine undergoes electrophilic addition to the new olefin forming a halonium ion which is subsequently ring-opened by the other guanidine. Formation of the oxazolidi-2-one, the third and last ring, occurs when the mixture is subjected to acetic acid which facilitates the decomposition of the boc group to a carboxylate which displaces the neighboring iodine atom by an S_N2 reaction. Overall, the reaction accomplishes the construction of a single stereoisomer by the formation of 2 C-N bonds, 1 C-O bond, and 3 rings.

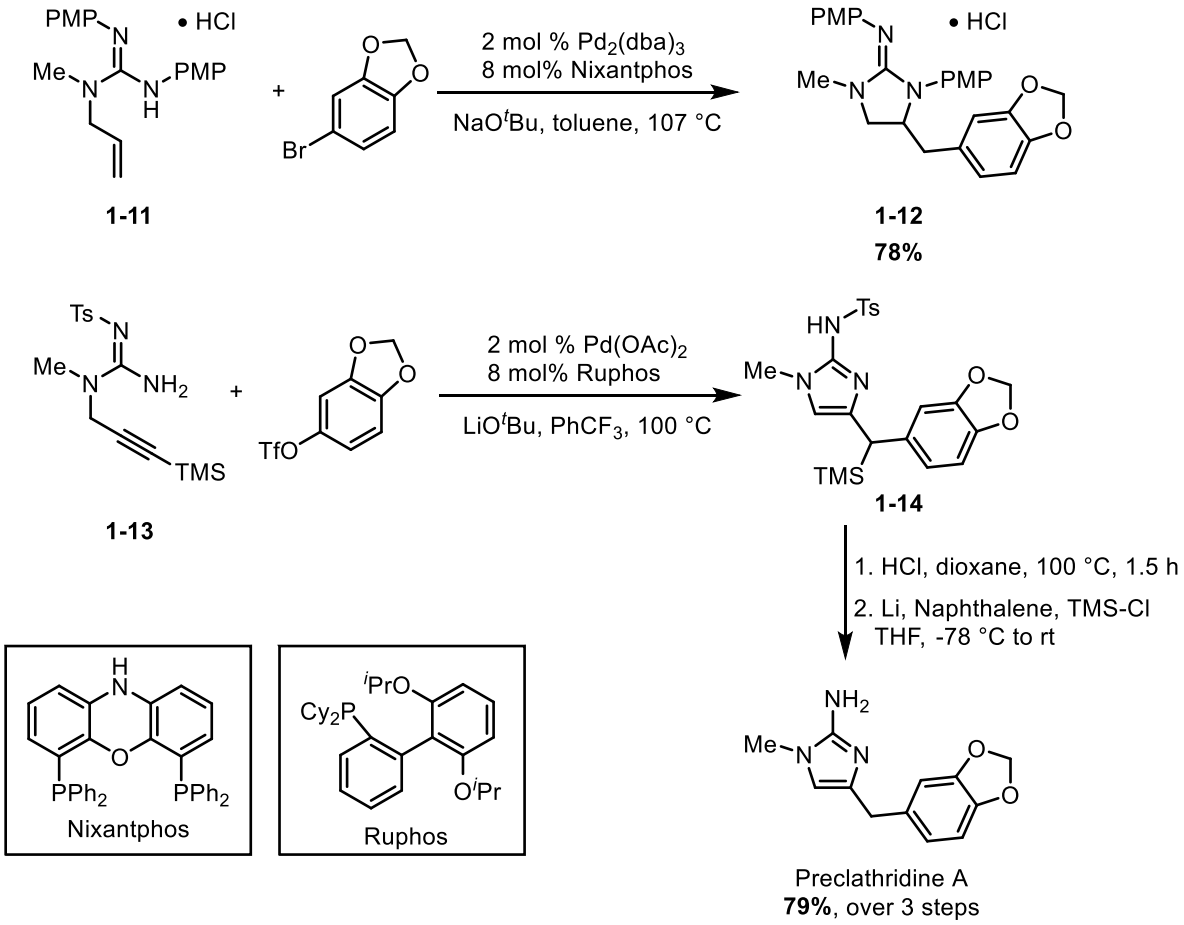
Scheme 1.3 Formation of Bicyclic Guanidine towards Araiosamine C



Recent work from the Baran group outlined an expeditious total synthesis of araiosamine C which utilized a sequential ring closure strategy for the synthesis of bicycle **1-10** (**Scheme 1.3**).[12] This natural product contains a unique densely functionalized topology bearing two cyclic guanidine units and three pendant bromoindole heterocycles (**Figure 1.1**). The Baran group set out to synthesize this unique structure despite it having no significant bioactivity. En route to the natural product, a novel guanylating reagent **1-8** was developed which chemoselectively guanylates the amino-alcohol at the primary amine. Then, the cyclic guanidine was formed by DDQ oxidation under "Yonemitsu-type" conditions[13] affording a crude

reaction mixture which was further reduced with DIBALH to form the hemiaminal in bicyclic guanidine **1-10**. From here, the natural product was formed in four subsequent steps (*not shown*).

Scheme 1.4 Pd-Catalyzed Synthesis of Cyclic Guanidines

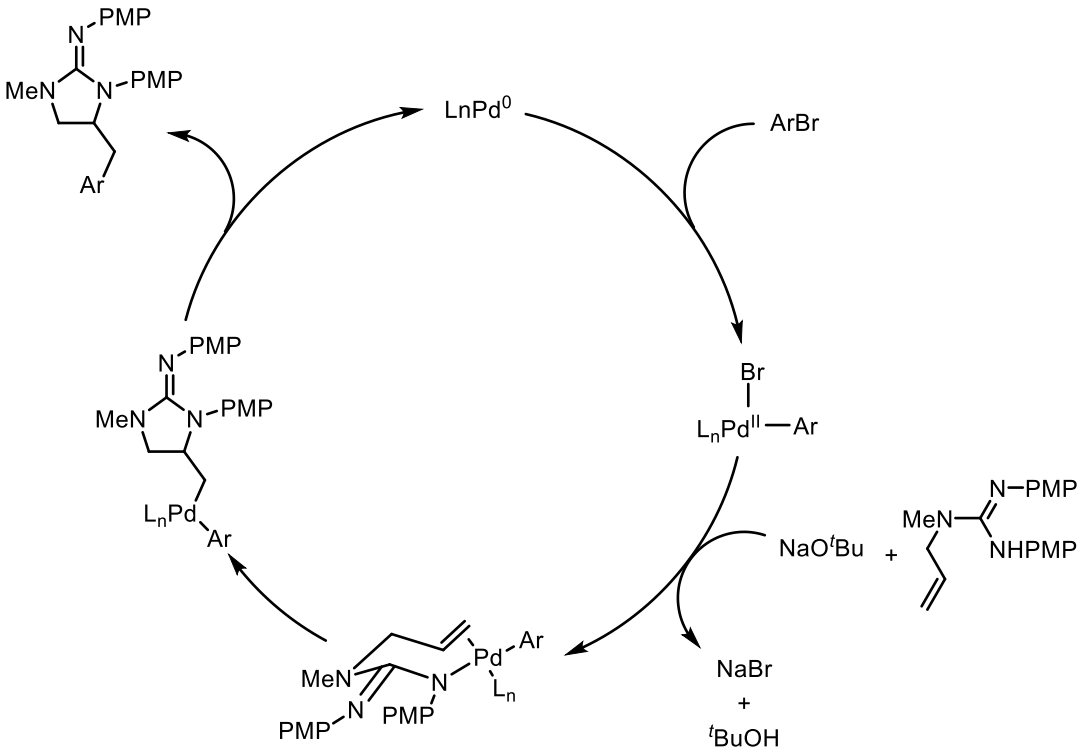


The Pd-catalyzed functionalization of olefins tethered to heteroatoms offers another potential strategy for synthesizing cyclic guanidines. This strategy has several advantages over existing methods for the formation of heterocycles including simple

protocols (catalysts can be weighed in air), opportunity for high stereoselectivity through well-defined transition states, and rapid generation of compound libraries by exchange of electrophilic coupling partners.[14] Because of these advantages, developing new methods for generating cyclic guanidines by Pd-catalyzed cyclization onto units of unsaturation is attractive.

Recently, Wolfe and coworkers demonstrated that guanidines protected with PMP groups can undergo Pd-catalyzed carboamination reactions, providing new cyclic guanidines in good yields (up to 99%) and moderate to good dr (2:1 dr up to 20: 1 dr) (**Scheme 1.4**).[15] The reaction exploits a catalyst derived from $Pd_2(dba)_3$ and the ligand Xantphos for achieving reactivity. Presumably, the reaction proceeds by initial oxidation addition to a Pd(0) complex which is followed by formation of an intermediate Pd-amido complex which engages migratory insertion and subsequent reductive elimination for formation of the heterocycle.[16] Efforts to render the reaction enantioselective were largely unsuccessful; the best enantiomeric ratio was generated by use of (*S*)-Phanephos (92% yield, 61:39 er).

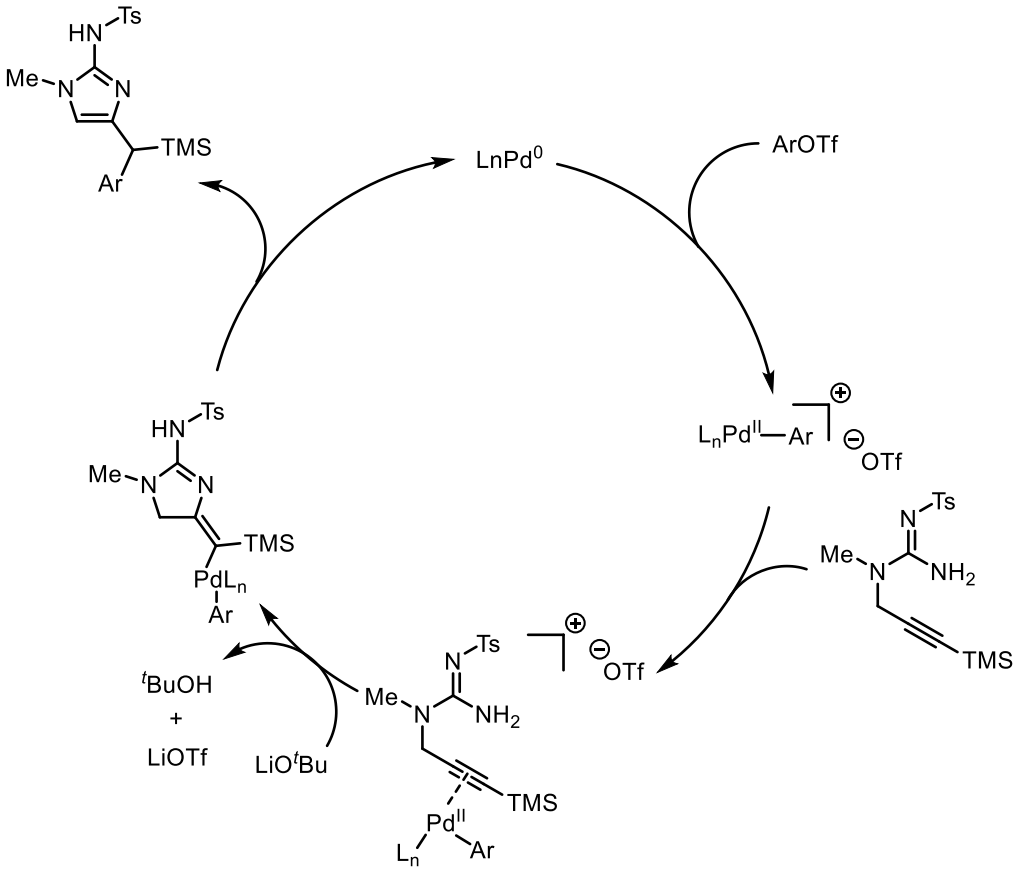
Figure 1.4 Catalytic Cycle for Pd-catalyzed Synthesis of Cyclic Guanidines by *Syn*-Aminopalladation Pathways



Additionally, Wolfe and coworkers have developed a new Pd-mediated protocol for the synthesis of 2-aminoimidazoles (**Scheme 1.4**). The formation of several new 2-aminoimidazoles (up to 97% yield) is achieved utilizing a catalyst derived from $Pd(OAc)_2$ and the ligand RuPhos.[17] This reaction proceeds by cyclization of a Ts-protected guanidine onto an alkyne under an *anti*-type mechanism in which the Pd preferentially coordinates to the alkyne facilitating backside attack of the electron deficient guanidine. This alkyl-Pd complex undergoes reductive elimination to afford a product which rapidly undergoes isomerization to generate the 2-aminoimidazole. The power of this method is further highlighted by the synthesis of three natural products from the same starting material simply by exchanging the electrophilic coupling partner. The synthesis of preclathridine A is shown above. The synthesis is completed after the Pd-mediated

cyclization by acidic removal of the TMS group followed by cleavage of the Ts group under reductive conditions.

Figure 1.5 Catalytic Cycle for Pd-catalyzed Synthesis of Cyclic Guanidines by *Anti*-Aminopalladation Pathways

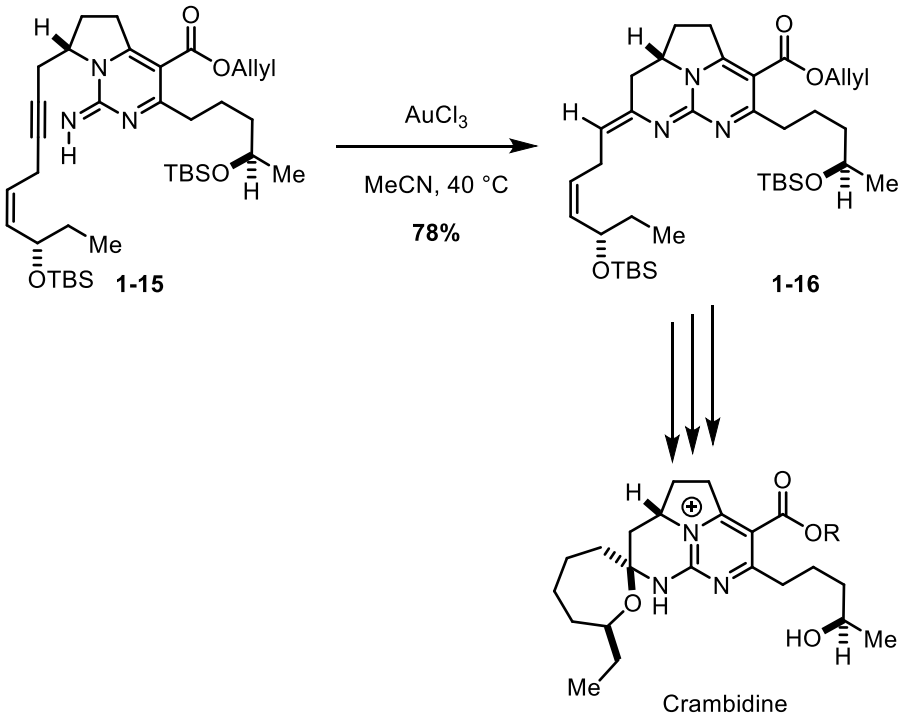


1.3 Hydroamination Protocols for the Synthesis of Cyclic Guanidines

The hydroamination of alkynes in the presence of transition metals is useful for the formation of cyclic guanidines because nucleophilic attack is facilitated by π-activation of the alkyne. This strategy has been elegantly utilized by Gin, Van der

Eckyen, and Looper for synthesizing different 5- and 6-membered cyclic guanidines as described below.

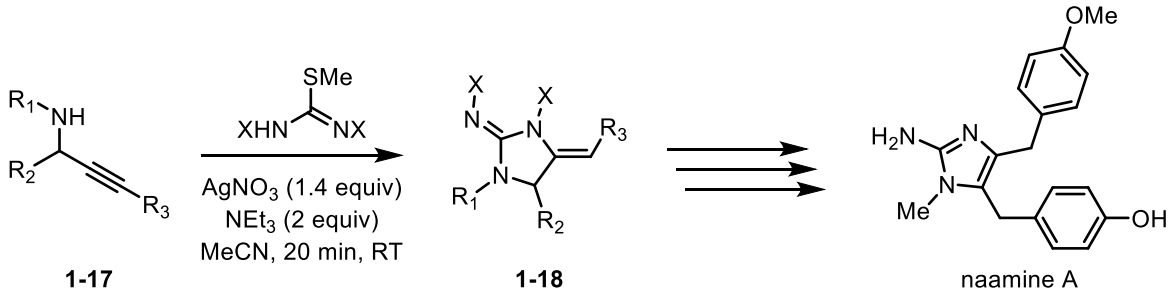
Scheme 1.5 Gin Total Synthesis of Crambidine



The sophisticated synthesis of crambidine by the Gin group[18] which utilizes an innovative [4+2] thioimidate-vinyl carbodiimide annulation strategy for formation of **1-16** also showcases a late stage Au-mediated cyclization of a guanidine onto an alkyne to close the tricyclic core (**Scheme 1.5**). The synthesis of **1-15** occurs in 5 steps from (*S*)-2-(*tert*-butylsilyloxy)butyraldehyde staging the penultimate cyclization of the tricyclic core. It should be noted that many strategies that accomplish the total synthesis of these types of tricyclic guanidines utilize a retrosynthesis which proceeds through this

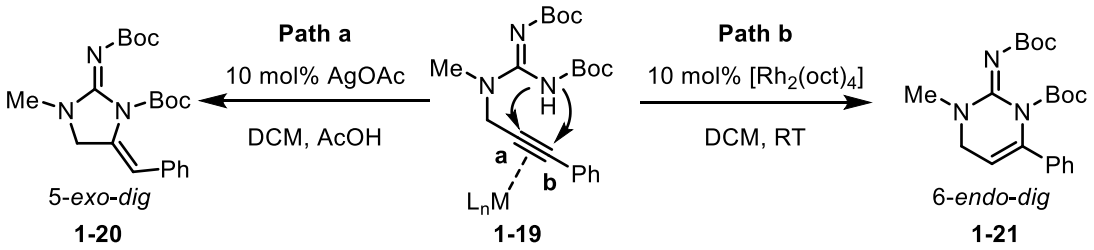
common bicyclic intermediate.[19] Here, the key step is accomplished with $AuCl_3$ serving as a Lewis acid to activate the alkyne for nucleophilic attack of the guanidine, thus closing the third ring of the tricylic core in 78% yield. Further transformations lead to the natural product Crambidine.

Scheme 1.6 Van der Eckyen Synthesis of 2-Aminoimidazoles by One-Pot Guanylation/Cyclization Sequence



In a second example, the Van der Eckyen group[20] demonstrated the utility of silver nitrate for facilitating a one-pot guanylation/cyclization sequence for generating cyclic guanidines bearing exocyclic alkenes. The silver nitrate serves two purposes in this reaction: facilitating the guanylation by assisting the leaving group ability of –SMe, and secondly, by activating the alkyne for nucleophilic attack. The reaction is competent for bis-protected guanidines bearing either Boc or Cbz protecting groups. Moreover, the reaction is highly successful proceeding in up to 100% yield. The utility of this transformation was showcased by the total synthesis of 6 different 2-aminoimidazole natural products including naamine A as shown in **Scheme 1.6**.

Scheme 1.7 Regioselective Hydroamination of bis-Boc Protected Guanidines



In addition to applications toward the synthesis of STX described above, the Looper group devised a regioselective method for performing hydroamination reactions of guanidines bearing tethered alkynes (**Scheme 1.7**).[21] This method accomplishes a 5-*exo-dig* cyclization utilizing AgOAc as a Lewis acid. The regioselectivity is altered by utilizing $[Rh_2(oct)_4]$ as a catalyst providing the product derived from the 6-*endo-dig* cyclization.

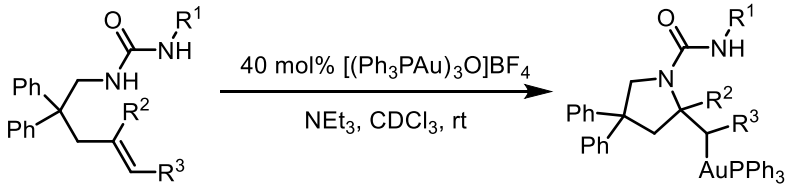
1.4. Hydroamination Reactions of Unactivated Alkenes for the Synthesis of Other Heterocycles

While the methods developed by the Gin, Van der Eckyen and Looper groups showcased successful hydroamination reactions of guanidines onto alkynes, no examples have been proffered for the direct cyclization of guanidines onto alkenes, even though metal-mediated hydroamination protocols have found widespread use in the literature for many other functional groups.

For instance, Widenhoefer and coworkers described the hydroamination of ethylene using a Pt catalyst as early as 2004.[22] In addition, the Widenhoefer group

accomplished the hydroamination of ureas across unactivated olefins using a catalytic amount of Au[P(^{t}Bu)$_2$(*o*-biphenyl)]Cl and AgOTf (5 mol%).[23] This reaction proceeds in great yield (up to 100% yield) and moderate dr (up to 5.5:1 dr) to form pyrrolidines and piperidine scaffolds. The reaction also tolerates 1,1-disubstituted alkenes in 92% yield.

Table 1.1. Aminoauration Reaction with Urea Substrates



1-22 **1-23**

Entry	R^1	R^2	R^3	Yield
1	^{t}Bu	H	H	**80**
2	Me	Me	H	**60**
3	Et	H	Ph	Trace

In a similar work, Toste and co-workers developed conditions for aminoauration reactions between ureas and unactivated olefins to form alkylgold(I) complexes with attached pyrrolidines (**Table 1.1**).[24] These complexes can undergo protodemetallation to afford the hydroamination products. The reaction proceeds in 2-14 h using 40 mol% $[(Ph_3PAu)_3O]BF_4$ in the presence of NEt_3 and $CDCl_3$. The substrate scope reveals some interesting aspects of this reaction. In terms of alkene substitution, 1,1-disubstituted alkenes were competent under the reaction conditions (Entry 2) to form tertiary amines, but 1,2-disubstituted were unable to engage the aminoauration reaction with either methyl or phenyl substitution at the 2 position (Entry 3 shows trace product for R^3 = Ph).

Moreover, forcing conditions (1 equiv of $[(Ph_3PAu)_3O]BF_4$ and 48 h reaction time) were able to generate 30% yield of the alkylgold(I) complex with a piperidine ring attached. All in all, this work provides a basis for Lewis acid-mediated hydroamination protocols, and moreover this work suggests which alkene substitutions will be fit for other Lewis acid-mediated cyclizations onto unactivated alkenes.

1.5 Conclusion

In this chapter, the current technologies available for creating cyclic guanidines are discussed by reviewing the current literature. The next chapter will outline the discovery and development of the first example of a metal-mediated hydroamination reaction to form cyclic guanidines by cyclization onto an unactivated alkene.

1.6 References

(1) (a) (1) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep*. **2008**, *25*, 919; (b) Berlinck, R. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A.E.; Romminger, S.; Morais, R.P.; Bandeira, K.; Mizuno, C.M. *Nat. Prod. Rep*. **2010**, *27*, 1871; (c) Berlinck, R.G.S.; Trindade-Silva, A.E.; Santos, M.F.C. *Nat. Prod. Rep*. **2012**, *29*, 1382; (d) Berlinck, R. G. S.; Romminger, S. *Nat. Prod. Rep*. **2016**, *33*, 456.

(2) Patil, A. D.; Kumar, N.V.; Kokke, W.C.; Bean, M.F.; Freyer, A.J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D.J.; Carte. B.; Breen, A.L.; Hertzberg, R.P.; Johnson, R.K.; Westley, J.W.; Potts, B.C.M. *J. Org. Chem*. **1995**, *60*, 1182.

(3) (a) Selig, P. *Synthesis*, **2013**, *45*, 703; (b) Leow, D.; Tan, C. –H. *Chem. Asian. J.* **2009**, *4*, 488; (c) Leow, D.; Tan, C. –H. *Synlett*, **2010**, 1589.

(4) Holmes, T.C.; May, A.E.; Zaleta-Rivera, K.; Ruby, J.G.; Skewes-Cox, P.; Fischbach, M.A.; DeRIsi, J.L.; Iwatsuki, M.; Ōmura, S.; Khosla, C. *J. Am. Chem. Soc*. **2012**, *134*, 17797.

(5) (a) Lehane, L. *Paralytic Shellfish Poisoning: A Review*. National Office of Animal and Plant Health, Agriculture, Fisheries and Forestry, Canberra, Australia, 2000. (b) Kao, C. Y.; Levinson, S. R. *Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel*; New York Academy of Sciences: New York, 1986.

(6) (a) Schantz, E. J.; Ghazarossian, V. E.; Schnoes, H. K.; Strong, F. M.;Springer, J. P.; Pezzanite, J. O.; Clardy, J. *J. Am. Chem. Soc*. **1975**, *97*, 1238; (b) Bordner, J.; Thiessen, W. E.; Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc*.**1975**, *97*, 6008.

(7) Tanino, H.; Nakata, T.; Kaneko, T.; Y. Kishi, *J. Am. Chem. Soc*. **1977**, *99*, 2818.

(8) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc*. **1984**, *106*, 5594.

(9) (a) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc*. **2006**, *128*, 3926; (b) Fleming, J.J.; McReynolds, M.D.; Du Bois, J. *J. Am. Chem. Soc*. **2007**, *129*, 9964.

(10) Iwamoto, O.; Shinohara, R.; Nagasawa, K. *Chem. Asian. J.* **2009**, *4*, 277.

(11) Bhonde, V.R.; Looper, R.E. *J. Am. Chem. Soc*. **2011**, *133*, 20172.

(12) Tian, M.; Yan, M.; Baran, P.S. *J. Am. Chem. Soc.* **2016**, *138*, 14234.

(13) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.

(14) (a) Schultz, D.M.; Wolfe, J.P. *Synthesis*. **2012**, *44*, 351; (b) Wolfe, J.P. *Eur. J. Org. Chem*. **2007**, 571.

(15) Zavesky, B.P.; Babij, N.R.; Wolfe, J.P. *Org. Lett.* **2013**, *15*, 5420.

(16) For mechanistic studies, see: (a) Neukom, J.D.; Perch, N.S.; Wolfe, J.P. *J. Am. Chem. Soc*. **2010**, *132*, 6276;(b) Neukom, J.D.; Perch, N.S.; Wolfe, J.P. *Organometallics*, **2011**, *30*, 1269.

(17) Zavesky, B.P.; Babij, N.R.; Wolfe, J.P. *Org. Lett.* **2014**, *16*, 4952.

(18) Perl, N.R.; Ide, N.D.; Prajapati, S.; Perfect, H.H.; Durón, S.G.; Gin, D.Y. *J. Am. Chem. Soc*. **2010**, *132*, 1802.

(19) For selected efforts towards the syntheses of polycyclic guanidine alkaloids, see: (a) Murphy, P.J.; Williams, H.L.; Hursthouse, M.B.; Abdul Malik, K.M. *J. Chem. Soc. Chem. Commun*. **1994**, 119; (b) Snider, B.B.; Chen, J.; Patil, A.D.; A. J. Freyer, *Tetrahedron Lett*. **1996**, 37, 6977; (c) Cohen, F.; Overman, L.E. *J. Am. Chem. Soc*. **2001**, *123*, 10782; (d) Overman, L.E.; Wolfe, J.P. *J. Org. Chem*. **2001**, *66*, 3167; (e) Aron, Z.D.; Overman, L.E. *Chem. Commun*. **2004**, 253; (f) Butters, M.; Davies, C.D.; Elliott, M.C.; Hill-Cousins, J.; Kariuki, B.M.; Ooi, L.-L.; Wood, J.L.; Wordingham, S.V. *Org. Biomol. Chem*. **2009**, *7,* 5001; (g) Evans, P.A.; Qin, J.; Robinson, J.E.; Bazin, B. *Angew. Chem*. **2007**, *119*, 7561; *Angew. Chem. Int. Ed*. **2007**, *46*, 7417. (h) Ishiwata, T.; Hino, T.; Koshino, H.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Org. Lett*. **2002**, *4*, 2921.

(20) Ermolat'ev, D.S.; Bariwal, J.B.; Steenackers, H.P.L.; De Keersmaecker, S.C.J.; Van der Eycken, E.V. *Angew. Chem. Int. Ed*. **2010**, *49*, 9465.

(21) Gainer, M. J.; Bennett, N.R.; Takahashi, Y.; Looper, R.E. *Angew. Chem. Int. Ed*. **2011**, *50*, 684.

(22) Wang, X.; Widenhoefer, R.A. *Organometallics*, **2004**, *23*, 1649. For the mechanism of this reaction, see: Bender, C.F.; Brown, T.J.; Widenhoefer, R.A. *Organometallics*, **2016**, *35*, 113.

(23) Bender, C.F.; Widenhoefer, R.A. **2006**, *8*, 5303.

(24) LaLonde, R.L. Brenzovich, Jr., W.E.; Tkatchouk, E.; Kelley, K.; Goddard, III, W.A.; Toste, F.D. *Chem Sci*. **2010**, *1*, 226.

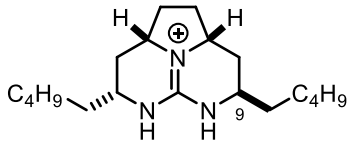
Chapter 2

Synthesis of Cyclic Guanidines via Silver-Catalyzed Intramolecular Alkene Hydroamination Reactions of *N*-Allylguanidines

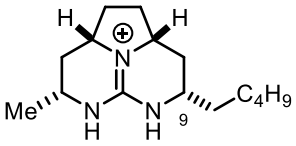
2.1 Introduction and Background

Inspiration for developing new methods for the synthesis of cyclic guanidines derives from interests in synthesizing the batzelladine alkaloids. The batzelladine alkaloids are defined by a guanidine functionality embedded within a tricyclic core that is decorated along the periphery by multiple stereocenters. Due to interest in these complex alkaloids, several groups have devoted efforts towards completing the synthesis of these natural products.[1]

Figure 2.1 Batzelladine Natural Products



merobatzelladine B



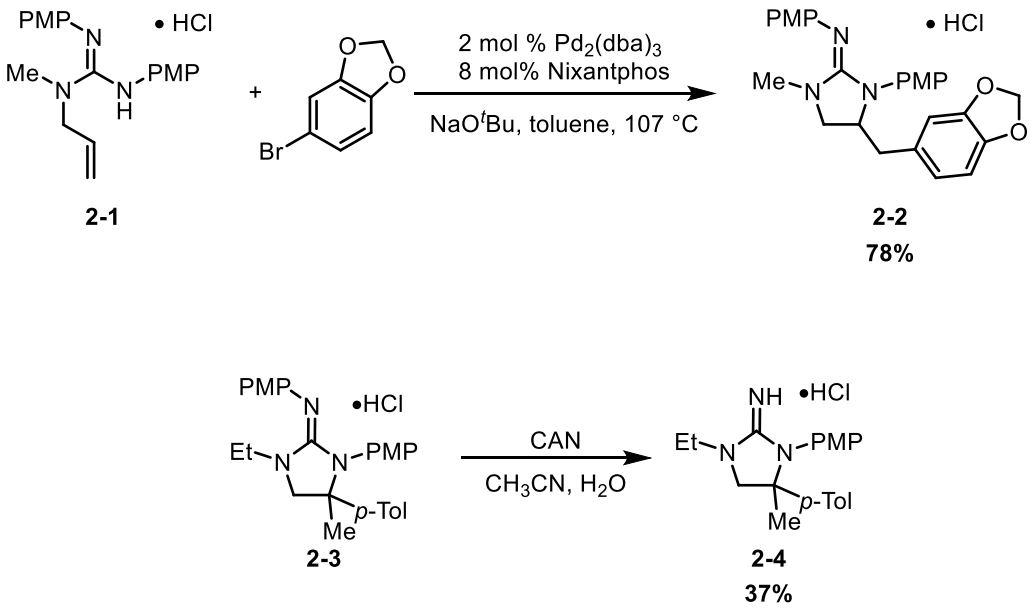
batzelladine K

Specifically, two strategies from the Wolfe group have been exploited towards the synthesis of two members of this family of natural products, merobatzelladine B and

batzelladine K (**Figure 2.1**).[2] Both methods rely on sequential Pd-catalyzed carboamination reactions, the second of which is a cyclization of a urea which forms the key bicyclic retron. The Pd carboamination reaction is attractive for the synthesis of these compounds because these reactions proceed with high stereoselectivity. While these methods have been successful in targeting these natural products, a more direct strategy which implements guanidines as nucleophilic components rather than ureas could shorten step-count and improve the overall efficiency of the reaction. As such, the Wolfe group has sought the development of Pd-catalyzed carboamination reactions by which utilize protected guanidines as nucleophiles.

As described in Chapter 1, two methods have been developed so far for the formation of cyclic guanidines by the Pd-catalyzed carboamination reaction. One method achieves formation of 2-aminoimidazoles by Pd-mediated cyclization of Ts-protected guanidines onto alkynes via an *anti*-type mechanism.[3] The other method produces saturated cyclic guanidines by cyclization of a bis PMP-protected guanidine onto a tethered alkene.[4] While this last method demonstrated great success in accomplishing the Pd-catalyzed carboamination reaction, the utility of this reaction suffered due to protecting group removability. Despite efforts to cleave the protecting groups, the best result only produced 37% of product **2-4** with one PMP group still appended (see **Scheme 2.1**). Due to this limitation, further studies on the competence of different cleavable protecting groups has been underway.

Scheme 2.1 Pd-Catalyzed Carboamination to Form Cyclic Guanidines



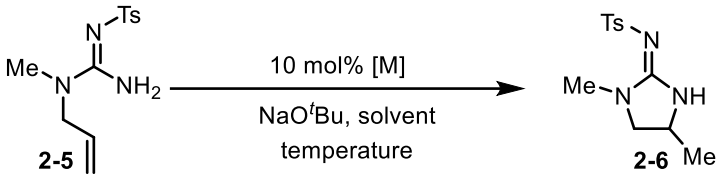
2.2 Discovery and Optimization

The discovery of the hydroamination reaction of Ts-protected guanidines onto tethered alkenes occurred while investigating the influence of silver salts on the development of cationic palladium complexes for the Pd-catalyzed carboamination reaction. Cationic palladium complexes were under investigation because the mechanism of the palladium carboamination reaction for the formation of cyclic sulfamides showed that judicious choice of reaction conditions like solvent, ligand, and base could divert mechanistic pathways by formation of such a cationic Pd complex.[5] In this regard, a *syn*-aminopalladation mechanism is operative for the carboamination reaction when aryl halides, non-polar solvents, and bidentate ligands like DPEPhos are used. Conversely, an *anti*-aminopalladation mechanism is operative when aryl triflates, polar solvents, and electron-rich Buchwald ligands are used. Discovering new avenues

by which the cationic palladium complex might be modified to promote *anti*-aminopalladation pathways could extend the synthetic utility of this divergent reactivity, and thus silver salts were under investigation. The literature suggested that the implementation of silver salts might generate a cationic Pd complex by abstraction of halides from the metal center.[6]

While studying the competence of tosyl-protecting groups for the Pd-catalyzed carboamination reaction in tandem with the use of silver salts for promoting cationic Pd complexes, a new hydroamination side product was isolated in 20% yield (along with about 50% Heck products and 13% starting material). Control reactions demonstrated that the palladium was unnecessary for the transformation to occur, but the presence of silver acetate (1 equiv) and base were required for high conversion.

Table 2.1 Optimization Studies for Ag-Catalyzed Hydroamination Reaction



Entry[a]	Catalyst	solvent	Temperature (°C)	Atmosphere	yield (%)
1	AgOAc	$PhCH_3$	100	N_2	<2%[c]
2	AgOTf	$PhCH_3$	100	N_2	14%[c]
3	AgOTf	$Ph(CH_3)_2$	138	N_2	40%[c]
4	AgOTf	$Ph(CH_3)_2$	138	N_2	45
5	Ag_2O	$Ph(CH_3)_2$	138	N_2	15
6	$Cu(OTf)_2$	$Ph(CH_3)_2$	138	N_2	25
7	CuI	$Ph(CH_3)_2$	138	N_2	18
8	$AuPPh_3OTf$	$Ph(CH_3)_2$	138	N_2	<2
9	AgOTf	$Ph(CH_3)_2$	138	O_2	70
10	$AgNO_3$	$Ph(CH_3)_2$	138	O_2	99[d]
11	$AgNO_3$	$PhCH_3$	40	O_2	<2[d]
12	$AgNO_3$	$PhCH_3$	80	O_2	99[d]
13	$AgNO_3$	$PhCH_3$	80	air	85[d]
14	$AgNO_3$	PhCl	80	air	99
15	$AgNO_3$	PhCl	80	O_2	99
16	$AgNO_3$	PhCl	80	N_2	60[e,f]
17	$AgNO_3$	PhCl	80	N_2	99[e,g]

[a]Conditions: 1.0 equiv of **X**, 1 equiv Na^{t}OBu, 10 mol % catalyst, solvent (0.1 M), 40-138 °C, 17-21 h. Reactions conducted on a 0.075-0.25 mmol scale. [b]Yields were determined by ^{1}H NMR analysis using phenanthrene as an internal standard. [c]The reaction was conducted in the presence of the ligand NiXantPhos (10 mol %). [d]The reactions were conducted at 0.033 M concentration. [e]The reaction was conducted in distilled and degassed chlorobenzene. [f]Reaction progress was stopped at 60% conversion (40% unreacted starting material). [g]The reaction was conducted using 1 equiv of $AgNO_3$.

A rigorous optimization proceeded to obtain synthetically useful yields for this transformation as shown in **Table 2.1**. First, attempts to render the reaction catalytic in silver were made by lowering the loading of AgOAc to 10 mol %, but this prevented the

formation of desired product. Switching to AgOTf[7] as catalyst improved the yield to 14%, and an increase in temperature to 138 °C (with solvent switch to xylenes) improved the yield further to 40% (**Table 2.1**, entry 2 and entry 3). At this point, the reaction was conducted without ligand, and the change in yield was negligible (45%) (**Table 2.1**, entry 4). Several other metal sources were tested but did not improve the yield (**Table 2.1**, entry 5 through entry 8). As a consequence, further improvements to the overall yield were impeded until the influence of oxygen on the reaction was considered.

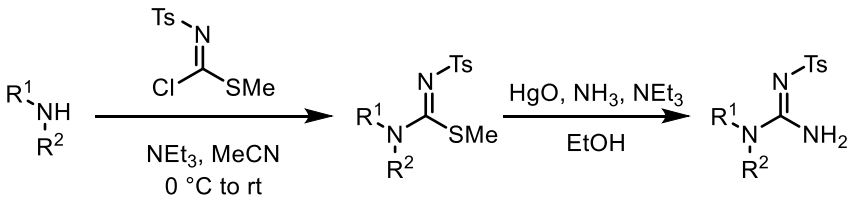
It was hypothesized that adventitious oxygen might be promoting the reaction, so the reaction was conducted under a balloon of oxygen. This improved the yield to 70% (**Table 2.1**, entry 9). From here, the temperature and solvent were optimized with the best yields being obtained at 80 °C in 0.1 M PhCl. The reaction could also proceed under ambient atmosphere through exposing the reaction with a needle pierced into the septum, but these reactions were not reproducible and were likely sensitive to humidity (**Table 2.1**, entry 13 and entry 14).

Two final control experiments were conducted to investigate the role of oxygen in the reaction. First, the reaction was conducted under an atmosphere of nitrogen in rigorously degassed and dried chlorobenzene proceeding to generate 60% of desired product which suggested that oxygen was unnecessary for catalyst turnover (**Table 2.1**, entry 16). Lastly, the reaction was conducted with a full equivalent of silver nitrate under a nitrogen environment which generated the desired product in 99% yield (**Table 2.1**, entry 17).

2.3 Substrate Scope and Limitations

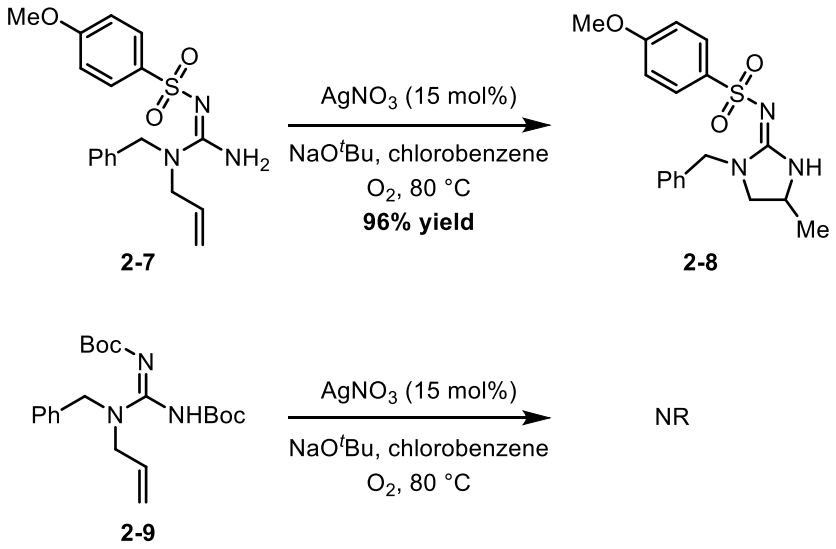
The substrates for the hydroamination reaction are readily made by a two-step protocol beginning with the desired allylamine (**Scheme 2.2**). First, methyl tosylcarbonochloridoimidothioate is reacted with an allylic amine to produce the intermediate carbimidothioate. This is reacted further with ammonia in the presence of mercury oxide in order to produce the desired guanidine.

Scheme 2.2. Substrate Synthesis



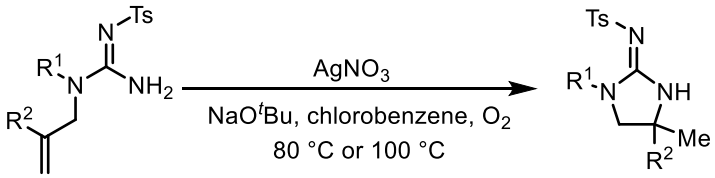
The substrate scope was first examined by exploring other suitable protecting groups (**Scheme 2.3**). The 4-methoxylphenylsulfonyl variant of the Ts group worked well under the optimized reaction conditions producing the desired product **2-8** in 96% yield. Unfortunately, substrate **2-9** failed to achieve desired reactivity leading to decomposition of starting material. This was disappointing because the boc group is readily cleaved to generate the free guanidine.

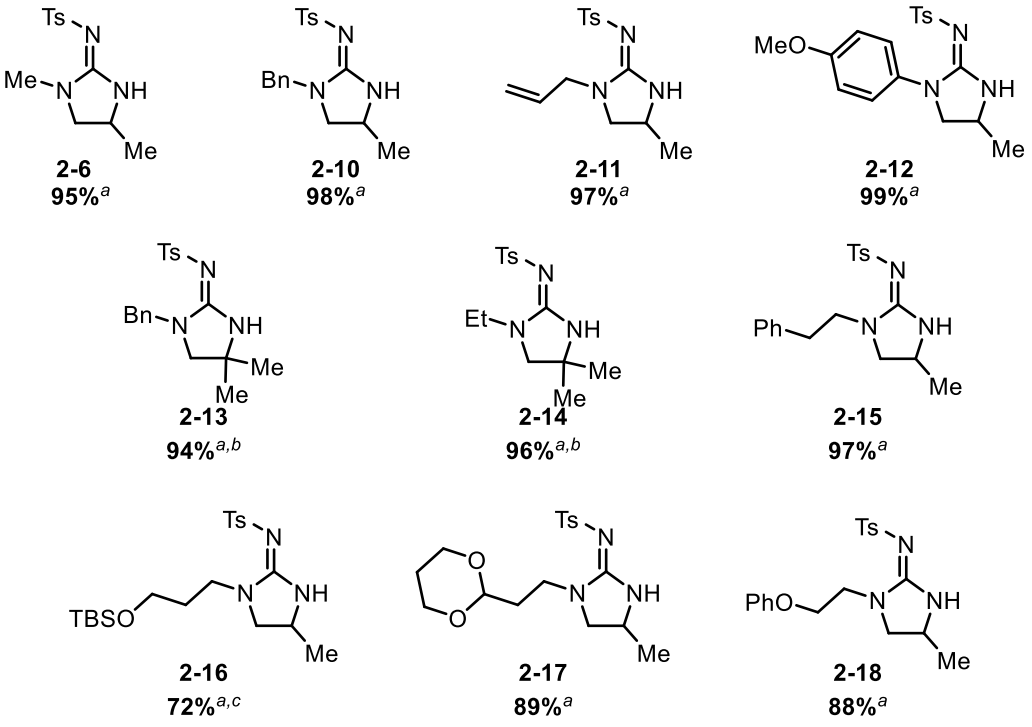
Scheme 2.3 Use of Other Protecting Groups



The substrate scope of the silver-catalyzed hydroamination reaction of tosyl-protected guanidines was evaluated by synthesizing several differentially substituted *N*-allyl guanidines and subjecting the substrates to the optimized reaction conditions (**Scheme 2.4**). Substrates bearing substitutions at the non-cyclizing nitrogen with a wide array of alkyl groups including methyl, benzyl, allyl, and *p*-methoxyphenyl were transformed with great yields (up to 99%). Hemiacetals and silyl protected ethers were also tolerated, although the latter afforded the desilylated product in 20% yield. The desilylated product was verified by subjecting **2-16** to TBAF deprotection. Quaternary centers were also generated by the cyclization of 1,1-disubstituted alkenes in high yields, although slightly more catalyst was required when reactions were conducted at higher reaction temperatures (100 °C).

Scheme 2.4 Substrate Scope



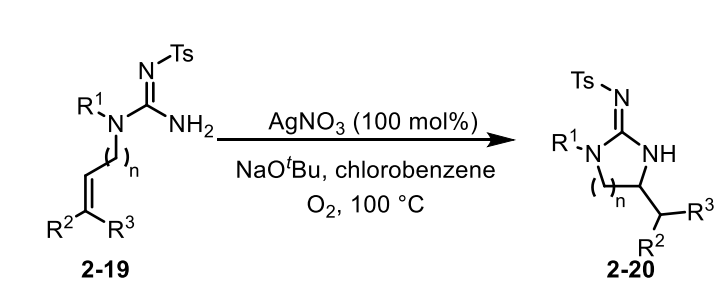


[a]Conditions: 1.0 equiv substrate, 1.0 equiv NaO^{t}Bu, 15 mol% $AgNO_3$, chlorobenzene (0.1 M), O_2 balloon, 80 °C, 16-18 h. Reactions were conducted on a 0.25 mmol scale. Isolated yields shown are an average of two or more experiments. [b]The reaction was conducted using 20 mol% $AgNO_3$ catalyst at 100 °C for 18 h. [c]Approximately 20% of the desilylated alcohol was generated.

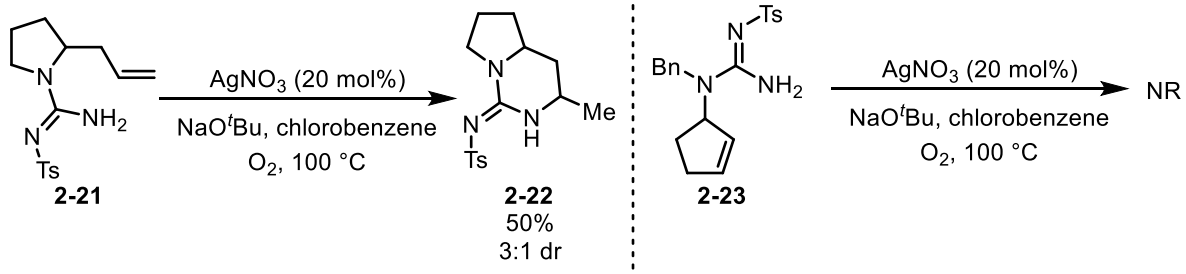
Substrates bearing 1,2-disubstituted alkenes did not cyclize efficiently under the hydroamination conditions as shown in **Scheme 2.5**. When the olefin was embedded within a ring system, the hydroamination reaction was still unsuccessful. Some moderate success was achieved when a cinnamyl group was tested, but the substrate

could not be separated from the starting material, and the reaction suffered from irreproducibility. Also, attempts to make larger rings failed when a homoallyl group was used rather than an allyl group. Attempts to perform the hydroamination reaction with **2-21** (which limits degrees of freedom due to the pyrrolidine backbone) were also made. While crude NMR data unveiled encouraging results, the starting material and product were once again inseparable. Attempts to increase the temperature or use more catalyst failed to improve this reaction.

Scheme 2.5 Substrates Bearing Limited or No Reactivity



Entry	n	R^1	R^2	R^3	yield (%)
1	1	Bn	Me	H	0
2	1	Bn	H	$H(CH_2)_2$	0
3	1	Bn	Me	Me	0
4	1	Me	Ph	H	50%
5	2	Bn	H	H	0

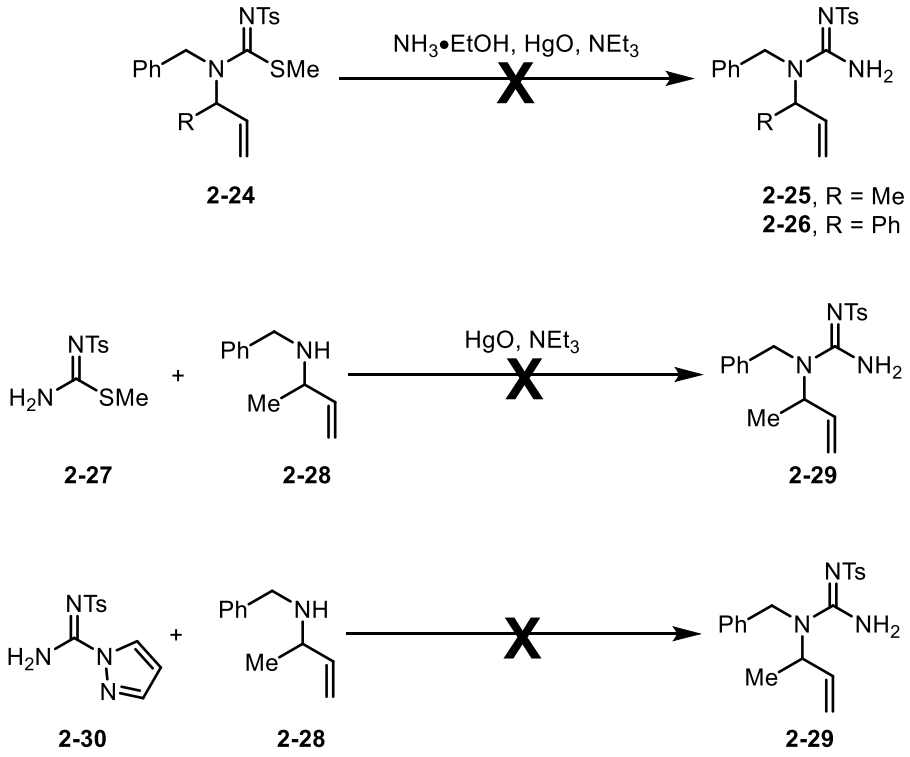


The limited reactivity of substituted alkenes, while disappointing, is not too surprising. First, studies have shown that formation constants for complexation of silver triflate decrease in the order: monosubstituted alkene > 1,1-disubstituted alkene > 1,2-

disubstituted alkene.[8] This limitation was also evidenced in the work of Toste and coworkers[9] for the aminoauration to form cyclic ureas which was described in Chapter 1. As a consequence, the failure of the silver-catalyzed hydroamination reaction to undergo intramolecular cyclization with 1,2-disubstituted olefins follows the precedent established in the literature.

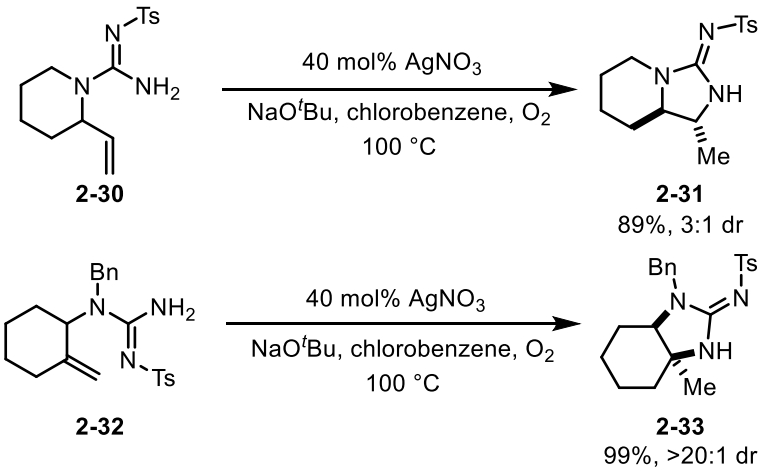
In order to explore the diastereoselectivity of this reaction, several attempts were made to construct substrates bearing an aliphatic alkene with allylic substitution (**Scheme 2.6**). The synthesis of *N*-allyl tosyl protected guanidine substrates with either a methyl group (**2-25**) or phenyl group (**2-26**) in the allylic position was attempted using normal conditions for synthesizing the substrates (guanylation of NH_3 in EtOH mediated by HgO) but failed to provide the desired compound, presumably due to steric congestion. Attempts to reverse the coupling partners by making methyl-N'-tosylcarbamimidothioate or *N*'-tosyl-1*H*-pyrazole-1-carboximidamide and coupling N-benzylbut-3-en-2-amine in the presence of HgO and trimethylamine were also met with failure.

Scheme 2.6 Unsuccessful Attempts to Synthesize Acyclic Substrates Bearing Allylic Substitution



Therefore, the diastereoselectivity of the reaction was examined for the hydroamination reaction to form bicylic guanidines. Successful hydroamination of guanidine **2-30** afforded the bicyclic guanidine **2-31** with modest diastereoselectivity (3:1 dr) but good yield (89%). The major diastereomer likely arises from the more favored chair-like transition state which positions the alkene in an equatorial position rather than axial position. Successful hydroamination of **2-32** bearing an exocyclic guandine was also successfully achieved with high dr (>20:1 dr) and high yield (99%).

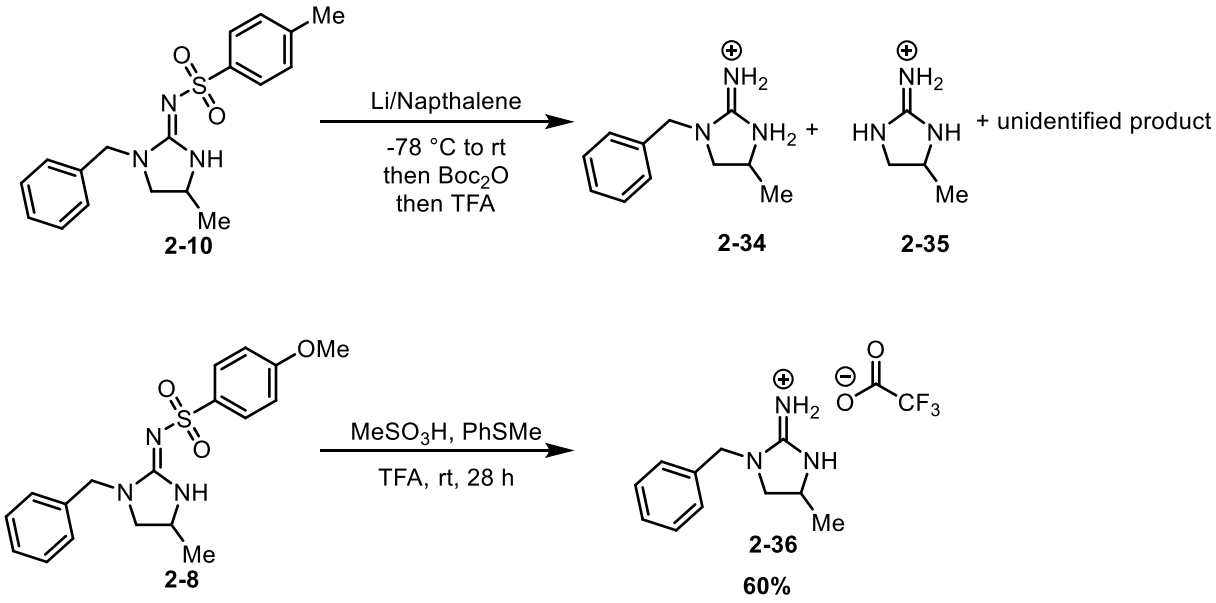
Scheme 2.7 Ag-Catalyzed Synthesis of Bicyclic Guanidines



2.4 Protecting Group Removal

The deprotection of the tosyl-protected cyclic guanidines was also briefly examined to demonstrate potential synthetic utility of the methodology. Previous work in the Wolfe group showed that the tosyl group is readily cleaved in the presence of lithium and napthalene to afford 2-aminoimidazoles.[3] This deprotection methodolgy was applied to the cyclic guanidines, but it ultimately proved impractical and unusable. The best results using this reductive strategy required additional Boc protection and removal to retrieve the products from the aqueous layer and verify their identities. In addition, the overall reaction led to overdeprotection by de-benzylation, producing mixtures of products that were difficult to separate by column chromatography.

Scheme 2.8 Protecting Group Removal



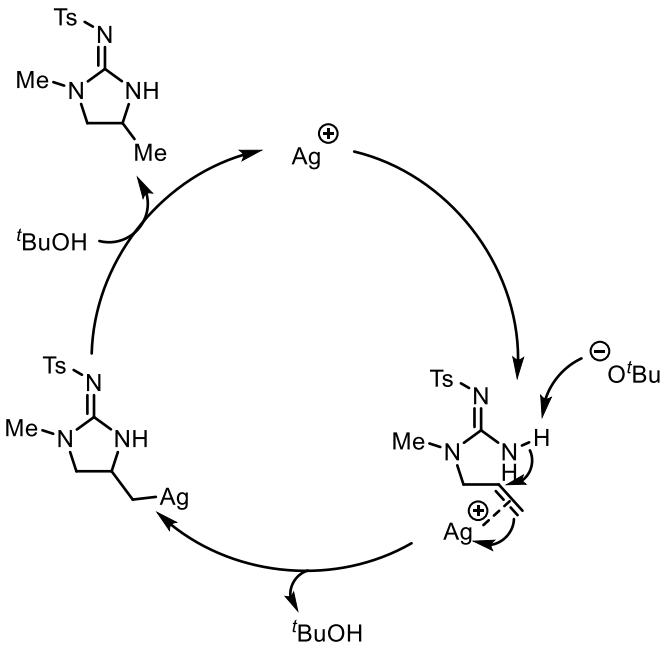
Instead, a more electron rich 4-methoxyphenyl sulfonyl protecting group was considered as a suitable substitute for accessing the free guanidine through deprotection. This variant of the Ts group exhibited high reactivity (96% as shown for **2-8** in **Scheme 2.3**) and likely performs similarly for all the substrates described in **Scheme 2.4**. Successful cleavage of the 4-methoxyphenyl sulfonyl protecting group was achieved using a method described by Du Bois and coworkers.[10] Reacting cyclic guanidine **2-8** with $MeSO_3H$, in the presence of thioanisole and TFA at room temperature afforded the deprotected guanidinium salt **2-36** in 60% yield.

2.5 Reaction Mechanism

The mechanism for this reaction is not currently well understood. At this point, the evidence suggests that the mechanism for this reaction proceeds via classical Lewis acid-mediated π activation as shown in **Figure 2.2**. This mechanistic manifold is also

proposed by Van Der Eckyen and coworkers in the similar Ag-mediated hydroamination of alkynes.[11] The proposed mechanism proceeds by coordination of Ag to the olefin. Then, deprotonation followed by nucleophilic attack of the alkene gives the alkyl-Ag complex which undergoes protonlysis to afford the cyclic guanidine and regenerate the catalyst.

Figure 2.2 Proposed Mechanism for Silver-Catalyzed Formation of Cyclic Guanidines



The role of oxygen is also not entirely clear. The oxygen most likely inhibits catalyst decomposition to Ag^0. It is known that $2AgNO_{3(l)}$ decomposes under heating to $2Ag(s) + O_{2(g)} + 2NO_{2(g)}$. It is plausible that oxygen simply slows this decomposition pathway by Le Chatelier's Principle. Experiments conducted during the optimization suggest that oxygen is not required for catalyst turnover. For instance, when the

reaction was conducted in rigorously dried and degassed chlorobenzene, the reaction proceeded to 60% conversion to product (6 turnovers) (See **Table 2.1**, entry 16). In addition, the reaction proceeded to completion under an atmosphere of $N_{2(g)}$ with 1 equiv of $AgNO_3$. Further studies would be needed to fully elucidate the role of oxygen in this reaction. In addition, using persulfate oxidants or inorganic nitrate salts might also serve the same purpose as oxygen gas, and if this reaction were to be constructed on a large scale, these methods might be preferred to the use of oxygen.

2.6 Conclusion

This chapter describes the first metal-catalyzed intramolecular alkene hydroamination reactions of guanidine nucleophiles. These transformations proceed in high yield generating a variety of five-membered cyclic guanidines containing a methyl substituent adjacent to the ring nitrogen atom.

Future directions for this project may include the following. First, the exact role of oxygen is not clear, so distinct mechanistic studies should be conducted to elucidate the role of oxygen. While a Lewis acid-mediated model in which oxygen simply slows the decomposition of silver is favored, a radical mechanism could still be operative. As such, re-visiting some of the early experiments conducted during optimization may provide insight. Oxygen could slow down the rate of decomposition for silver nitrate, but what is the influence of oxygen on silver triflate? Also, synthesizing a substrate which bears a cyclopropyl protecting group on the guanidine may unveil whether a radical is formed at the guanidine center. In addition, further explorations of viable protecting groups will expand the substrate scope of the reaction and perhaps improve the

synthetic utility of the reaction. Finally, devising a method for the synthesis of acyclic substrates which bear allylic substitution would provide much desired information regarding the diastereoselectivity of the reaction. Lastly, while all literature precedent for hydroamination reactions indicate that 1,2-disubstituted alkenes fail to undergo this type of reaction, the successful cyclization of a nucleophile onto a 1,2-disubstituted alkene would be a significant achievement.

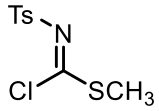
2.7 Experimental Section

General Considerations: All reactions were carried out under a nitrogen atmosphere using flame-dried or oven dried glassware unless otherwise noted. Silver nitrate was purchased from Sigma Aldrich. Toluene, THF, dichloromethane, ether and triethylamine were purified using a GlassContour solvent purification system. Chlorobenzene was purchased from Fisher Scientific and used as received. Ratios of diastereomers were determined by ^{1}H NMR analysis of the crude material. Dimethyl tosylcarbonimidodithioate[12] and *N*^{1}-Allyl-*N*^{2},*N*^{3}-Bis(*tert*-butoxycarbonyl)-*N*^{1}-methylguanidine[13] were prepared according to published procedures. Yields refer to isolated compounds that are estimated to be $\geq$95% pure as judged by ^{1}H NMR. The yields reported in **2.7 Experimental Section** describe the result of a single experiment,

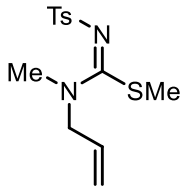
whereas yields reported in **Table 2.1**, **Scheme 2.4**, and **Scheme 2.7** are average yields of two or more experiments.

Experimental Procedures and Characterization Data for Substrates

Synthesis of Substrates:



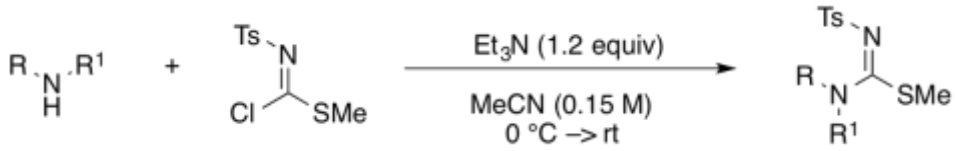
Methyl tosylcarbonochloridoimidothioate:[14] The title compound was prepared using a procedure developed by DuBois and coworkers.[9] A 250 mL flame dried flask equipped with a stirbar was purged with nitrogen and charged with dimethyl tosylcarbonimidodithioate (18 mmol, 5.0 g) and dichloromethane (60 mL). While stirring, sulfuryl chloride (36.5 mmol, 3 mL) was added dropwise to the mixture. The resulting mixture was heated to reflux for 3 h, and then cooled to rt. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes as eluant to afford 4.0 g (85%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, J = 8.1 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 2.47 (s, 3 H), 2.44 (s, 3 H).



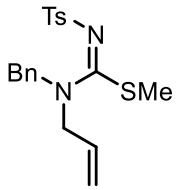
Methyl *N*-allyl-*N*-methyl-*N*'-tosylcarbamimidothioate: A 15 mL thick-walled glass pressure tube equipped with a Teflon screwcap was flame dried, cooled under a stream

of nitrogen and charged with *N*-methylprop-2-en-1-ylamine (8.0 mmol, 770 μL), dimethyl tosylcarbonimidodithioate (7.3 mmol, 2.0 g), and toluene (5 mL). The mixture was heated to 100 °C with stirring for 3 h, then was cooled to rt and the methanethiol byproduct was removed by purging the flask with nitrogen. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes as eluant to afford 2.17 g (91%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, *J* = 7.8 Hz, 2 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 5.61–5.70 (m, 1 H), 5.16 (dd, *J* = 10.3, 1.2 Hz, 1 H), 5.09 (dd, *J* = 17.1, 1.2 Hz, 1 H), 4.08 (d, *J* = 5.6 Hz, 2 H), 3.07 (s, 3 H), 2.45 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.4, 142.0, 141.6, 130.8, 129.0, 125.8, 118.9, 55.8, 38.9, 21.4, 17.7.

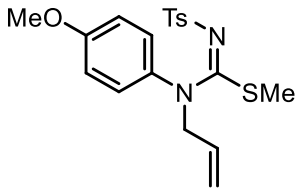
General Procedure 1 for Preparation of carbamimidothioates.



A flame dried flask equipped with a stirbar was cooled under a stream of nitrogen and charged with methyl tosylcarbonochloridoimidothioate (or derivative) and anhydrous acetonitrile (0.15 M). The mixture was cooled to 0 °C then triethylamine (1.2 equiv.) was added dropwise. The appropriate secondary amine (1.1 equiv.) was then added dropwise as a solution in acetonitrile (1.5 mL/mmol of amine). The reaction mixture was then warmed to rt and stirred overnight (18 h). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel using hexanes/diethyl ether/ethyl acetate as eluant.

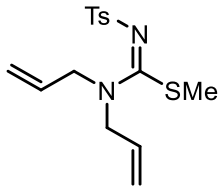


Methyl *N*-allyl-*N*-benzyl-*N′*-tosylcarbamimidothioate: General procedure 1 was used to acylate *N*-benzylprop-2-en-1-ylamine[15] (3.6 mmol, 530 mg) with methyl tosylcarbonochloridoimidothioate (1.5 mmol, 396 mg). This procedure afforded 434 mg (77%) of the title compound as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.24–7.32 (m, 3 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.13 (d, *J* = 6.4 Hz, 2 H), 5.69 (ddt, *J* = 16.8, 10.5, 5.8 Hz, 1 H), 5.19 (d, *J* = 10.0 Hz, 1 H), 5.08 (d, *J* = 17.1 Hz, 1 H), 4.69 (s, 2 H), 4.06 (d, *J* = 5.6 Hz, 2 H), 2.72 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.5, 141.8, 135.3, 131.1, 129.2, 128.9, 128.0, 127.7, 126.0, 119.2, 53.3, 52.8, 21.5, 18.6, (one peak is missing due to incidental equivalence).

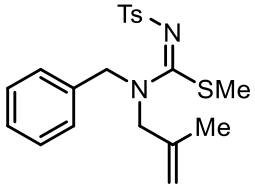


Methyl *N*-allyl-*N*-(4-methoxyphenyl)-*N′*-tosylcarbamimidothioate: General procedure 1 was used to acylate *N*-allyl-4-methoxyaniline[16] (5.0 mmol, 820 mg) with methyl tosylcarbonochloridoimidothioate (4.5 mmol, 1.2 g). This procedure afforded 1.70 g (97%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 7.02–7.10 (m, 2 H), 6.83–6.90 (m, 2 H), 5.69–5.79 (m, 1 H), 5.03 (dd, *J* = 10.1, 0.9 Hz, 1 H), 4.88 (dd, *J* = 17.1, 1.2 Hz, 1 H), 4.30 (d, *J* = 6.4 Hz, 2 H), 3.78 (s, 3 H), 2.37 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (175 MHz,

$CDCl_3$) δ 167.4, 159.5, 141.9, 141.6, 134.6, 131.4, 129.2, 129.1, 126.2, 119.5, 114.7, 57.9, 55.5, 21.5, 18.3.

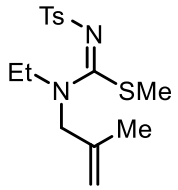


Methyl *N,N*-diallyl-*N′*-tosylcarbamimidothioate: General procedure 1 was used to acylate diallylamine (6.0 mmol, 580.0 mg) with methyl tosylcarbonochloridoimidothioate (5.5 mmol, 1.44 g). This procedure afforded 1.65 g (93%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.82 (m, 2 H), 7.19–7.25 (m, 2 H), 5.66–5.76 (m, 2 H), 5.19 (dd, *J* = 10.1, 1.1 Hz, 2 H), 5.11 (dd, *J* = 17.1, 1.2 Hz, 2 H), 4.08 (d, *J* = 5.6 Hz, 4 H), 2.68 (t, *J* = 1.7 Hz, 3 H), 2.38 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.2, 142.0, 141.9, 131.4, 129.2, 126.1, 119.1, 53.0, 21.6, 18.5.

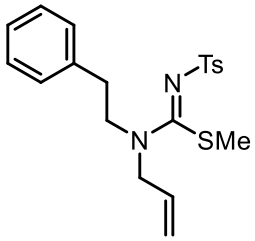


Methyl *N*-benzyl-*N*-(2-methylallyl)-*N′*-tosylcarbamimidothioate: General procedure 1 was used to acylate N-benzyl-2-methylprop-2-en-1-amine[17] (3.75 mmol, 605 mg) with methyl tosylcarbonochloridoimidothioate (3.4 mmol, 900 mg). This procedure afforded 1.33 g (91%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.21–7.32 (m, 3 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.09–7.13 (m, 2 H), 4.90 (s, 1 H), 4.68 (d, *J* = 18.1 Hz, 3 H), 4.01 (s, 2 H), 2.70 (s, 3 H), 2.33 (s, 3 H), 1.60

(s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.0, 141.7, 141.7, 138.7, 135.3, 129.1, 128.8, 127.9, 127.7, 126.0, 113.2, 55.3, 53.1, 21.4, 20.0, 18.6.



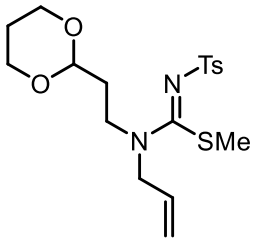
Methyl *N*-ethyl-*N*-(2-methylallyl)-*N'*-tosylcarbamimidothioate: General procedure 1 was used to acylate *N*-ethyl-2-methylprop-2-en-1-ylamine (6.27 mmol, 622 mg) with methyl tosylcarbonochloridoimidothioate (5.7 mmol, 1.5 g). This procedure afforded 1.7 g (90%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 4.78 (s, 1 H), 4.62 (s, 1 H), 3.96 (s, 2 H), 3.40 (q, *J* = 7.1 Hz, 2 H), 2.61 (s, 3 H), 2.29 (s, 3 H), 1.51 (s, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.8, 142.0, 141.4, 139.0, 128.9, 125.7, 112.7, 55.7, 45.7, 21.3, 19.8, 18.3, 12.5.



Methyl-*N*-allyl-*N*-phenethyl-*N*'-tosylcarbamimidothioate: A flame-dried flask was cooled under a stream of nitrogen and charged with allylamine (150 mmol, 11.3 mL) and potassium carbonate (90 mmol, 12.5 g). Neat (2-bromoethyl)benzene was added dropwise via syringe pump to the vigorously stirring mixture over 45 minutes and the

resulting mixture was stirred at rt overnight. The mixture was then filtered through celite, the celite was washed with dichloromethane (3 x 30 mL), and then the solvent was removed under reduced pressure. The crude secondary amine was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford *N*-phenethylprop-2-en-1-amine (3.95 g, 82%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.29–7.34 (m, 2 H), 7.18–7.25 (m, 3 H), 5.90 (ddt, *J* = 16.9, 10.5, 6.1 Hz, 1 H), 5.16 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.09 (dq, *J* = 10.3, 1.4 Hz, 1 H), 3.28 (dt, *J* = 5.9, 1.4 Hz, 2 H), 2.87–2.93 (m, 2 H), 2.81–2.85 (m, 2 H), 1.32 (s, br, 1 H).

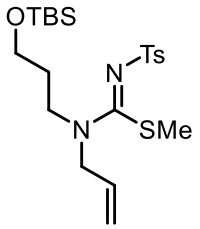
General procedure 1 was used to acylate *N*-phenethylprop-2-en-1-amine (7.7 mmol, 1.24 g) with methyl tosylcarbonochloridoimidothioate (7 mmol, 1.85 g). This procedure afforded 2.67 g (98%) of the title compound as a viscous oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2 H), 7.16–7.28 (m, 5 H), 6.96 (s, br, 2 H), 5.66–5.73 (m, 1 H), 5.19 (d, *J* = 10.2 Hz, 1 H), 5.11 (d, *J* = 17.2 Hz, 1 H), 4.06 (d, *J* = 5.1 Hz, 2 H), 3.58 (s, br, 2 H), 2.77–2.83 (m, 2 H), 2.75 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.6, 142.1, 141.9, 137.9, 131.6, 129.3, 128.8, 128.7, 126.8, 126.2, 118.9, 54.3, 52.7, 33.9, 21.6, 18.7.



Methyl-*N*-[2-(1,3-dioxan-2-yl)ethyl]-*N*-allyl-*N*'-tosylcarbamimidothioate: A flame-dried flask was cooled under a stream of nitrogen and charged with allylamine (200

mmol, 15.0 mL) and potassium carbonate (120 mmol, 17.0 g). Neat 2-(2-bromoethyl)-1,3-dioxane (40 mmol, 5.5 mL) was added dropwise via syringe pump to the vigorously stirring mixture over 60 minutes and the resulting mixture was stirred at rt overnight. The mixture was then filtered through celite, the celite was washed with dichloromethane (3 x 30 mL), and then the solvent was removed under reduced pressure. The crude secondary amine was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 3.32 g (48%) of *N*-[2-(1,3-dioxan-2-yl)ethyl]prop-2-en-1-amine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 17.2, 10.3, 6.0 Hz, 1 H), 5.15 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.06 (dq, *J* = 10.3, 1.4 Hz, 1 H), 4.62 (t, *J* = 5.0 Hz, 1 H), 4.05–4.10 (m, 2 H), 3.65–3.81 (m, 2 H), 3.22 (dt, *J* = 6.0, 1.4 Hz, 2 H), 2.70 (t, *J* = 6.8 Hz, 2 H), 1.96–2.15 (m, 1 H), 1.79 (td, *J* = 6.8, 5.1 Hz, 2 H), 1.43 (s, br, 1 H), 1.32 (dtt, *J* = 13.4, 2.6, 1.3 Hz, 1 H)

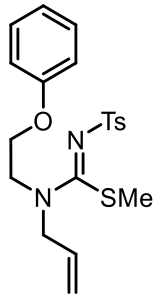
General procedure 1 was used to acylate *N*-(2-(1,3-dioxan-2-yl)ethyl)prop-2-en-1-amine (7.7 mmol, 1.32 g) with methyl tosylcarbonochloridoimidothioate (7.0 mmol, 1.32 g). This procedure afforded 2.77 g (99%) of the title compound as a viscous oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2 H), 7.19–7.24 (m, 2 H), 5.65–5.72 (m, 1 H), 5.16 (d, *J* = 10.2 Hz, 1 H), 5.10 (d, *J* = 17.0 Hz, 1 H), 4.45 (s, br, 1 H), 4.09 (d, *J* = 3.2 Hz, 2 H), 4.04 (dd, *J* = 11.1, 4.9 Hz, 2 H), 3.68 (td, *J* = 12.3, 2.0 Hz, 2 H), 3.55 (t, *J* = 6.8 Hz, 2 H), 2.71 (s, 3 H), 2.38 (s, 3 H), 1.97–2.06 (m, 1 H), 1.80–1.85 (m, 2 H), 1.31 (d, *J* = 13.5 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.8, 142.2, 141.7, 131.6, 129.2, 126.1, 118.8, 99.9, 67.0, 53.9, 46.3, 33.1, 25.8, 21.6, 18.6.



Methyl-*N*-allyl-*N*-{3-[(*tert*-butyldimethylsilyl)oxy]propyl}-*N*'-tosylcarbamimidothioate: A flame-dried flask was cooled under a stream of nitrogen and charged with allylamine (150 mmol, 11.3 mL) and potassium carbonate (90 mmol, 12.5 g). Neat (3-bromopropoxy)(*tert*-butyl)dimethylsilane[18] (30 mmol, 7.6 mL) was added dropwise via syringe pump to the vigorously stirring mixture over 50 minutes and the resulting mixture was stirred at rt overnight. The mixture was then filtered through celite, the celite was washed with dichloromethane (3 x 30 mL), and then the solvent was removed under reduced pressure. The crude secondary amine was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 4.45 g (65%) of *N*-{3-[(*tert*-butyldimethylsilyl)oxy]propyl}prop-2-en-1-amine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.97 (m, 1 H), 5.15 (dd, *J* = 17.2, 1.7 Hz, 1 H), 5.06 (dd, *J* = 10.3, 1.4 Hz, 1 H), 3.67 (t, *J* = 6.1 Hz, 2 H), 3.23 (dt, *J* = 6.0, 1.4 Hz, 2 H), 2.68 (t, *J* = 6.9 Hz, 2 H), 1.69 (t, *J* = 6.5 Hz, 2 H), 1.34 (s, br, 1 H), 0.86 (s, 9 H), 0.03 (s, 6 H).

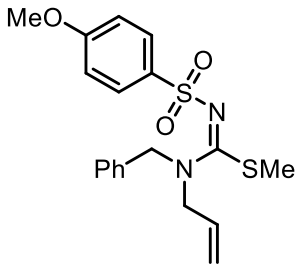
General procedure 1 was used to acylate *N*-{3-[(*tert*-butyldimethylsilyl)oxy]propyl}prop-2-en-1-amine (7.7 mmol, 1.77 g) with methyl tosylcarbonochloridoimidothioate (7.0 mmol, 1.85 g). This procedure afforded 3.2 g (99%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 5.66–5.75 (m, 1 H), 5.17 (d, *J* = 10.0 Hz, 1 H), 5.11 (dd, *J* = 17.1, 1.0 Hz, 1 H), 4.11 (d, *J* = 5.4 Hz, 2 H), 3.48–3.55 (m, 4 H), 2.71 (s, 3 H), 2.38 (s, 3 H), 1.69–1.76 (m, 2 H), 0.86 (s, 9 H), 0.0 (m, 6 H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 166.9, 142.3, 141.7, 131.7, 129.2, 126.1, 118.9, 60.2, 54.2, 48.4, 30.9, 26.0, 21.6, 18.6, 18.4, -5.3.

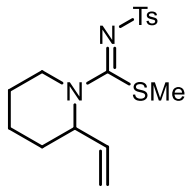


Methyl-*N*-allyl-*N*-(2-phenoxyethyl)-*N*'-tosylcarbamimidothioate: A flame-dried flask was cooled under a stream of nitrogen and charged with allylamine (150 mmol, 11.3 mL) and potassium carbonate (90, 12.5 g). A solution of (2-bromoethoxy)benzene (30 mmol, 6.0 g) was added dropwise as a solution in anhydrous DMF (6 mL) via syringe pump to the vigorously stirring mixture over 70 minutes and the resulting mixture was stirred at rt overnight. The mixture was then filtered through celite, the celite was washed with dichloromethane (3 x 30 mL), and then the solvent was removed under reduced pressure. The dichloromethane solution was then transferred to a separatory funnel and washed with 5% lithium chloride solution (60 mL) and brine (60 mL). The organic layer was dried with sodium sulfate, and then the solvent was removed under reduced pressure. The crude secondary amine was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 4.92 g (92%) of *N*-(2-phenoxyethyl)prop-2-en-1-amine as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.32 (m, 2 H), 6.90–6.99 (m, 3 H), 5.90–5.99 (m, 1 H), 5.23 (dq, *J* = 17.1, 1.7 Hz, 1 H), 5.13 (dq, *J* = 10.3, 1.4 Hz, 1 H), 4.08–4.12 (t, *J* = 5.0 Hz, 2 H), 3.35 (dt, *J* = 6.0, 1.4 Hz, 2 H), 3.01–3.05 (t, *J* = 5.0 Hz, 2 H), 1.70 (s, 1 H).

General procedure 1 was used to acylate *N*-(2-phenoxyethyl)prop-2-en-1-amine (7.7 mmol, 1.36 g) with methyl tosylcarbonochloridoimidothioate (7.0 mmol, 1.85 g). This procedure afforded 2.6 g (92%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2 H), 7.19–7.29 (m, 4 H), 6.96 (t, *J* = 7.3 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 2 H), 5.71–5.81 (m, 1 H), 5.22 (d, *J* = 10.3 Hz, 1 H), 5.15 (d, *J* = 17.1 Hz, 1 H), 4.31 (d, *J* = 5.1 Hz, 2 H), 4.01 (t, *J* = 5.4 Hz, 2 H), 3.83 (t, *J* = 5.3 Hz, 2 H), 2.73 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.2, 158.2, 142.0, 141.9, 131.5, 129.7, 129.3, 126.1, 121.4, 118.9, 114.4, 65.7, 55.2, 50.2, 21.6, 18.8.

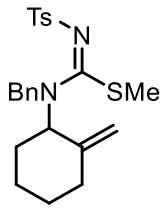


Methyl *N*-allyl-*N*-benzyl-*N′*-[(4-methoxyphenyl)sulfonyl]carbamimidothioate: General procedure 1 was used to acylate N-benzylprop-2-en-1-amine[15] (4.2 mmol, 620 mg) with methyl [(4-methoxyphenyl)sulfonyl]carbonochloridoimidothioate[10] (3.8 mmol, 1.05 g). This procedure afforded 1.44 g (97%) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.84 (m, 4 H), 7.23–7.31 (m, 7 H), 7.10–7.15 (m, 4 H), 6.83–6.89 (m, 5 H), 5.64–5.73 (m, 2 H), 5.18 (dd, *J* = 10.3, 1.0 Hz, 2 H), 5.07 (dd, *J* = 17.2, 0.9 Hz, 2 H), 4.69 (s, 5 H), 4.06 (d, *J* = 5.9 Hz, 5 H), 3.79 (s, 7 H), 2.71 (s, 7 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.2, 161.8, 136.7, 135.3, 131.2, 128.9, 128.0, 127.9, 127.7, 119.1, 113.7, 55.5, 53.3, 52.8, 18.6.



Methyl *N*-tosyl-2-vinylpiperidine-1-carbimidothioate: A round bottom flask equipped with a stirbar was charged with *tert*-butyl 2-vinylpiperidine-1-carboxylate[19] (6 mmol, 1.27 g) dichloromethane (30 mL) and trifluoracetic acid (6.0 mL). The reaction was stirred at rt until the boc group had been completely cleaved as judged by ^{1}H NMR analysis. The solvent was removed under reduced pressure, to afford 2-vinylpiperidinium trifluroacetate, which was used without further purification.

The crude 2-vinylpiperidinium trifluroacetate was converted to the title compound using a slight modification of general procedure 1 by addition to a stirring solution of methyl tosylcarbonochloridoimidothioate (5.5 mmol, 1.5 g) and triethylamine (13.2 mmol, 1.8 mL, 2.4 equiv.) in acetonitrile (0.15 M). This procedure afforded 1.4 g (75% over two steps) of the title compound as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 5.68 (ddd, *J* = 17.4, 10.6, 4.0 Hz, 1 H), 5.19–5.25 (m, 1 H), 5.19 (s, br, 1 H), 5.01–5.11 (m, 1 H), 4.30 (d, *J* = 13.7 Hz, 1 H), 3.10 (td, *J* = 13.1, 2.9 Hz, 1 H), 2.43 (s, 3 H), 2.33 (s, 3 H), 1.76–1.84 (m, 1 H), 1.40–1.74 (m, 5 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.4, 141.9, 141.6, 134.7, 129.1, 126.0, 117.8, 58.2, 45.8, 29.1, 25.7, 21.4, 19.3, 17.7.



Methyl *N*-benzyl-*N*-(2-methylenecyclohexyl)-*N'*-tosylcarbamimidothioate: A round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with 2-(benzylamino)cyclohexan-1-ol[20] (11.7 mmol, 2.4 g), potassium carbonate (12.9 mmol, 1.78 g) and THF (15 mL). The mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (12.9 mmol, 2.8 g) was added in one portion. The reaction mixture was warmed to rt and stirred until the starting material had been completely consumed as judged by TLC analysis. The mixture was then filtered through celite, the celite was rinsed with ether (2 x 50 mL), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 3.2 g (89 %) of *tert*-butyl benzyl(2-hydroxycyclohexyl)carbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.37 (m, 4 H), 7.21–7.25 (m, 1 H), 4.41 (s, br, 2 H), 3.87 (s, br, 1 H), 3.52 (s, br, 1 H), 2.04 (s, 1 H), 1.68 (s, br, 4 H), 1.44 (s, 9 H), 1.11–1.31 (m, 4 H).

A round bottom flask was flame dried, cooled under a stream of nitrogen, and charged with *tert*-butyl benzyl(2-hydroxycyclohexyl)carbamate (10.0 mmol, 3.0 g) and DMSO (20 mL). The mixture was stirred at rt and triethylamine (142 mmol, 20.0 mL) was added followed by a solution of sulfur trioxide pyridine complex (48 mmol, 7.6 g) in DMSO (30 mL). The mixture was stirred at rt until the starting material had been completely consumed as judged by TLC analysis, then water (50 mL) and ether (50 mL) were added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined and washed with water (3 x 50 mL) and brine (1 x 50 mL). The organic layers was then dried with sodium sulfate, filtered, and the solvent was removed

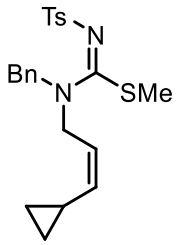
under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 2.9 g (95 %) of *tert*-butyl benzyl(2-oxocyclohexyl)carbamate. NMR analysis indicated the presence of impurities in the product. However, this material was carried on without further purification. The material was found to exist as a ca 2:1 mixture of rotamers based on ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.38 (m, 5 H), 4.58–4.83 (m, 1.5 H), 4.28–4.41 (m, 0.5 H), 4.04 (d, *J* = 17.8 Hz, 0.5 H), 3.83–3.95 (m, 0.5 H) 1.50–2.37 (m, 8 H), 1.35 (s, br, 9 H).

A flame dried round bottom flask equipped with a stirbar was charged with potassium *tert* butoxide (20.0 mmol, 2.2 g) and ether (70 mL). Solid methyltriphenylphosphonium bromide (20.0 mmol, 7.1 g) was added and the color of the solution became orange. The reaction mixture was stirred at rt for1 h, and then a solution of *tert*-butyl benzyl(2-oxocyclohexyl)carbamate (10 mmol, 3.03 g) in ether (20 mL) was added. The mixture was stirred at rt until the starting material had been completely consumed as judged by TLC analysis. Water (50 mL) was added, the mixture was transferred to a separatory funnel, and the layers separated. The aqueous layer was extracted with ether (1 x 50 mL) and hexanes (4 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfated, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 2.53 g of *tert*-butyl benzyl(2-methylenecyclohexyl)carbamate (84% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.33 (m, 2 H), 7.17–7.25 (m, 3 H), 4.78 (s, 1 H), 4.56 (s, br, 2 H), 4.07–4.16 (m, 1 H), 2.43 (d, *J* = 12.9 Hz, 1 H), 2.00–2.16 (m, 1 H), 1.74 (s,

br, 3 H), 1.40 (s, br, 11 H), 1.12–1.28 (m, 2 H).

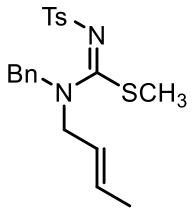
A round bottom flask equipped with a stirbar was charged with *tert*-butyl benzyl(2-methylenecyclohexyl)carbamate (7.3 mmol, 2.2 g), dichloromethane (37 mL), and trifluoracetic acid (7.3 mL). The resulting solution was stirred at rt until the starting material had been completely consumed as judged by ^{1}H NMR analysis. The solvent was then removed under reduced pressure, and the crude *N*-benzyl-2-methylenecyclohexylammonium trifluoroacetate product was dissolved in acetonitrile (8 mL), and then was converted to the title compound using a slight modification of general procedure 1 by addition of this solution to a separate stirring solution of methyl tosylcarbonochloridoimidothioate (6.2 mmol, 1.6 g) and triethylamine (22.0 mmol, 3.1 mL, 2.4 equiv.) in acetonitrile (40 mL) at 0 °C. This procedure afforded 2.2 g (70% over two steps) of the title compound as a viscous oil. The product appears to exist as a mixture of conformers, and contains some impurities. This material was used without further purification. Due to the complexity of the carbon NMR spectrum, all visible peaks are reported: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, br, 2 H), 7.16–7.32 (m, 4 H), 7.07 (d, *J* = 6.3 Hz, 3 H), 5.12 (d, *J* = 16.8 Hz, 1 H), 5.02 (d, *J* = 10.0 Hz, 1 H), 4.74–4.82 (m, 1 H), 4.44 (s, 1 H), 4.30 (d, *J* = 12.9 Hz, 1 H), 2.74 (s, 3 H), 2.27–2.43 (m, 4 H), 1.77–2.04 (m, 1 H), 1.62–1.74 (m, 3 H), 1.04–1.42 (m, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.4, 141.8, 141.6, 137.1, 129.0, 128.9, 128.6, 128.3, 127.9, 127.1, 126.1, 126.0, 110.1, 107.2, 64.5, 59.4, 51.5, 46.0, 35.0, 33.7, 32.0, 26.7, 25.7, 24.9, 24.2, 21.5, 20.4, 19.0, 18.8.



(*2Z*)-Methyl *N*-benzyl-*N*-(-3-cyclopropylallyl)-*N′*-tosylcarbamimidothioate: A flame dried round bottom flask was charged with potassium *tert*-butoxide (7.5 mmol, 840 mg) and ether (30 mL). Solid (cyclopropylmethyl)triphenylphosphonium bromide[21] (7.5 mmol, 3.0 g) was added and the color of the solution became orange. This mixture was stirred at rt for 1 h, and then *tert*-butyl benzyl(2-oxoethyl)carbamate[22] (5 mmol, 1.2 g) was added in a solution in ether (10 mL). The resulting mixture was stirred at rt until the starting material had been completely as judged by TLC analysis. Then, water (30 mL) was added, the mixture was transferred to a separatory funnel, and the layers were separated. The organic layers were combined, dried over anhydrous sodium sulfated, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 1.44 g (99%) of (Z)-*tert*-butyl benzyl(3-cyclopropylallyl)carbamate.

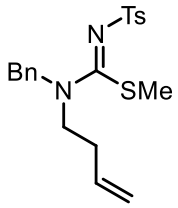
A round bottom flask equipped with a stirbar was charged with (Z)-*tert*-butyl benzyl(3-cyclopropylallyl)carbamate (4.2 mmol, 1.20 g), dichloromethane (20 mL), and trifluoracetic acid (4.2 mL). The resulting solution was stirred at rt until the starting material had been completely consumed as judged by ^{1}H NMR analysis. The solvent was then removed under reduced pressure, and the crude (*Z*)-*N*-benzyl-3-cyclopropylprop-2-en-1-aminium 2,2,2-trifluoroacetate was dissolved in acetonitrile (5 mL), and then was converted to the title compound using a slight modification of general

procedure 1 by addition of this solution to a separate stirring solution of tosylcarbonochloridoimidothioate (4.2 mmol, 1.1 g) and triethylamine (9.1 mmol, 1.3 mL, 2.4 equiv.) in acetonitrile (20 mL). This procedure afforded 1.2 g (70%) over two steps of the title compound as a viscous oil. The compound was isolated as an 1:3 mixture of *E:Z* alkene diastereomers as judged by ^{1}H NMR analysis. Data are for the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2 H), 7.22–7.32 (m, 3 H), 7.13–7.21 (m, 4 H), 5.22 (dt, *J* = 10.6, 7.1 Hz, 1 H), 4.92 (t, *J* = 10.4 Hz, 1 H), 4.73 (s, 2 H), 4.21 (d, *J* = 7.0 Hz, 2 H),2.71 (s, 3 H), 2.35 (s, 3 H), 1.17–1.28 (m, 1 H), 0.63–0.73 (m, 2 H), 0.26–0.36 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.4, 141.9, 141.6, 134.7, 129.1, 126.0, 117.8, 58.2, 45.8, 29.1, 25.7, 21.4, 19.3, 17.7.



(*E*)-Methyl *N*-benzyl-*N*-(-but-2-en-1-yl)-*N'*-tosylcarbamimidothioate: A round bottom flask equipped with a stirbar was charged with benzylamine (96 mmol, 10.5 mL) and potassium carbonate (24 mmol, 3.3 g). The mixture was stirred at rt and neat crotyl bromide (20 mmol, 2.0 mL, 85:15 *E:Z*) was added slowly dropwise. The resulting mixture was heated to 70 °C with stirring for 14 h. The mixture was then cooled to rt, filtered through celite, and the celite was washed with ethyl acetate (50 mL). The solvent was removed under reduced pressure, and then the crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to afford 2.56 g (79%) of (*E*)-*N*-benzylbut-2-en-1-ylamine as a yellow oil.

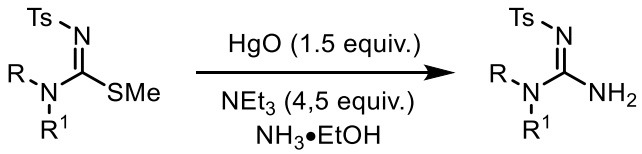
General procedure 1 was used to acylate (*E*)-*N*-benzylbut-2-en-1-ylamine (6.05 mmol, 980 mg) with methyl tosylcarbonochloridoimidothioate (5.5 mmol, 1.4 g). This procedure afforded 2.04 g (85%) of the title compound as a viscous oil. The compound was isolated as an 85:15 mixture of *E:Z* alkene diastereomers as determined by ^{1}H NMR analysis. ^{1}H NMR data are for the major isomer. ^{13}C NMR data are listed as observed, as it was not possible to rigorously assign some peaks to one isomer vs. the other: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.2 Hz, 2 H), 7.31–7.21 (m, 3 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.11 (d, *J* = 6.1 Hz, 2 H), 5.54–5.43 (m, 1 H), 5.36–5.24 (m, 1 H), 4.66 (s, 2 H), 3.97 (d, *J* = 6.1 Hz, 2 H), 2.71 (s, 3 H), 2.34 (s, 3 H), 1.63 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.4, 142.0, 141.8, 135.5, 131.2, 129.5, 129.2, 128.9, 128.0, 127.9, 127.7, 126.1, 126.0, 124.0, 123.7, 53.5, 53.1, 52.4, 47.2, 21.5, 18.6, 18.6, 17.8, 13.1.



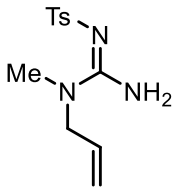
Methyl-*N*-benzyl-*N*-(but-3-en-1-yl)-*N*'-tosylcarbamimidothioate: General procedure 1 was used to acylate *N*-benzylbut-3-en-1-amine[23] (10 mmol, 1.6 g) with methyl tosylcarbonochloridoimidothioate (5 mmol, 1.3 g). This procedure afforded 1.74 g (90%) of the title compound as a viscous oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.26–7.32 (m, 3 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.13 (d, *J* = 7.0 Hz, 2 H), 5.53–5.62 (m, 1 H), 4.99 (d, *J* = 10.2 Hz, 1 H), 4.95 (d, = 17.0 *J* Hz, 1 H), 4.73 (s, br, 2 H), 3.47 (t, *J* = 7.3 Hz, 2 H), 2.76 (s, 3 H), 2.36 (s, 3 H), 2.23 (q, *J* = 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$,

175 MHz) δ 167.3, 141.9, 141.8, 135.5, 134.0, 129.2, 129.0, 128.1, 127.6, 126.1, 117.8, 54.5, 50.3, 32.0, 21.6, 18.8.

General Procedure 2 for preparation of *N*-allylguanidine substrates:

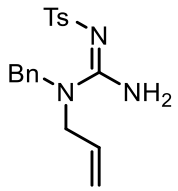


A flame-dried round bottom flask equipped with a stir bar was cooled under a stream of N_2 and charged with the appropriate carbamimidothioate (1 equiv), mercuric oxide (1.5 equiv), and triethylamine (4.5 equiv), followed by a 2 M solution of NH_3 in ethanol (20-40 equiv NH_3). The flask was capped with a greased glass stopper and the mixture was stirred at rt for 3 days. The solution was then filtered through celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography using dichloromethane/methanol as eluant.

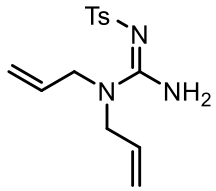


***N*-{[Allyl(methyl)amino](amino)methylene}-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl *N*-allyl-*N*-methyl-*N*'-tosylcarbamimidothioate (7.2 mmol, 2.14 g) to the title compound using mercuric oxide (10.8 mmol, 2.3 g), triethylamine (18.9 mmol, 4.6 mL), and NH_3 (75 mL, 2 M solution in ethanol). This procedure afforded 1.5 g (78%) of the title compound as a colorless solid,

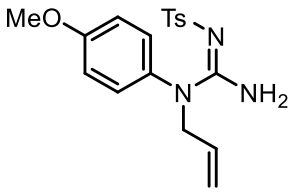
mp 121–125 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 6.17 (s, br, 2 H), 5.64–5.76 (m, 1 H), 5.19 (d, *J* = 10.3 Hz, 1 H), 5.11 (dd, *J* = 17.2, 1.1 Hz, 1 H), 3.97 (d, *J* = 4.2 Hz, 2 H), 2.94 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 141.9, 141.3, 132.0, 129.3, 126.1, 117.7, 52.3, 21.6, one peak is missing due to incidental equivalence; IR (neat) 3407.0, 1629.8, 1557.6, 1481.7, 1252.3 cm^{-1}; MS (ESI+) 268.1118 (268.1114 calcd for $C_{12}H_{17}N_3O_2S$, M + H^+).



***N*-{[Allyl(benzyl)amino](amino)methylene}-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl *N*-allyl-*N*-benzyl-*N′*-tosylcarbamimidothioate (2.9 mmol, 1.1 g) to the title compound using mercuric oxide (4.4 mmol, 962 mg), triethylamine (13.3 mmol, 1.9 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 800 mg (79%) of the title compound as a colorless solid, mp 118–121 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2 H), 7.23–7.29 (m, 3 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.08–7.15 (m, 2 H), 6.26 (s, br, 2 H), 5.63–5.73 (m, 1 H), 5.19 (d, *J* = 10.3 Hz, 1 H), 5.13 (d, *J* = 17.1 Hz, 1 H), 4.57 (s, 2 H), 3.90 (s, br, 2 H), 2.39 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.4, 141.9, 141.2, 136.2, 131.9, 129.2, 128.9, 127.9, 127.5, 126.1, 118.1, 51.3, 50.4, 21.6. IR (neat) 3414.0, 3319.8, 1624.2, 1539.9, 1487.5 cm^{-1}; MS (ESI+) 344.1430 (344.1427 calcd for $C_{18}H_{21}N_3O_2S$, M + H^+).

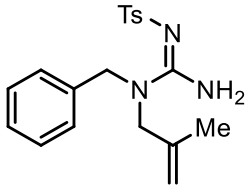


***N*-[Amino(diallylamino)methylene]-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl *N,N*-diallyl-*N′*-tosylcarbamimidothioate (3.8 mmol, 1.22 g) to the title compound using mercuric oxide (5.6 mmol, 1.2 g), triethylamine (17.1 mmol, 2.4 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 1.05 g (95%) of the title compound as a colorless solid, mp 114–118 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 6.19 (s, br, 2 H), 5.73 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 2 H), 5.19 (d, *J* = 10.3 Hz, 2 H), 5.13 (d, *J* = 17.2, 2 H), 3.93 (s, br, 4 H), 2.38 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.3, 141.9, 141.3, 132.3, 129.2, 126.1, 118.1, 50.5, 21.6; IR (neat) 3414.6, 3316.6, 1616.7, 1540.7, 1490.8 cm^{-1}; MS (ESI+) 294.1274 (294.1271 calcd for $C_{14}H_{19}N_3O_2S$, $M + H^+$).



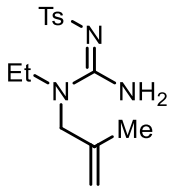
***N*-{[Allyl(4-methoxyphenyl)amino](amino)methylene}-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl *N*-allyl-*N*-(4-methoxyphenyl)-*N′*-tosylcarbamimidothioate (3.1 mmol, 1.22 g) to the title compound using mercuric oxide (4.7 mmol, 1.0 g), triethylamine (14.0 mmol, 2.0 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 900 mg (81%)

of the title compound as a colorless solid. mp 105–109 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2 H), 7.22–7.28 (m, 2 H), 7.07–7.11 (m, 2 H), 6.89–6.95 (m, 2 H), 5.74–5.84 (m, 1 H), 5.04 (dd, *J* = 10.0, 1.2 Hz, 1 H), 4.97 (dd, *J* = 17.1, 1.5 Hz, 1 H), 4.29 (d, *J* = 6.4 Hz, 2 H), 3.81 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.9, 155.5, 142.0, 141.2, 133.1, 131.9, 129.7, 129.3, 126.2, 118.5, 115.6, 55.7, 53.9, 21.6 IR (neat) 3446.3, 3330.1, 1607.5, 1506.2 cm^{-1}; MS (ESI+) 360.1380 (360.1376 calcd for $C_{18}H_{21}N_3O_3S$, $M + H^+$).



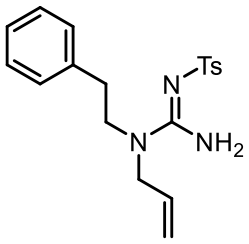
***N*-{Amino[benzyl(2-methylallyl)amino]methylene}-4-methylbenzenesulfonamide:**

General procedure 2 was used for the conversion of methyl *N*-benzyl-*N*-(2-methylallyl)-*N'*-tosylcarbamimidothioate (2.57 mmol, 998 mg) to the title compound using mercuric oxide (3.85 mmol, 834 mg), triethylamine (11.6 mmol, 1.6 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 577 mg (63%) of the title compound as a colorless solid, mp 98–102 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2 H), 7.23–7.29 (m, 3 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.09–7.14 (m, 2 H), 6.25 (s, br, 2 H), 4.93 (s, 1 H), 4.80 (s, 1 H), 4.59 (s, br, 2 H), 3.79 (s, br, 2 H), 2.40 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.8, 141.9, 141.3, 139.5, 136.2, 129.2, 129.0, 128.0, 127.7, 126.1, 112.9, 53.4, 51.4, 21.6, 19.9; IR (neat) 3414.2, 3320.8, 1616.8, 1534.0, 1490.7 cm^{-1}; MS (ESI+) 358.1586 (358.1584 calcd for $C_{19}H_{23}N_3O_2S$, $M + H^+$).



***N*-{Amino[ethyl(2-methylallyl)amino]methylene}-4-methylbenzenesulfonamide:**

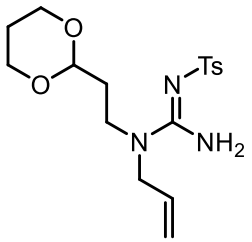
General procedure 2 was used for the conversion of methyl *N*-ethyl-*N*-(2-methylallyl)-*N'*-tosylcarbamimidothioate (4.6 mmol, 1.50 g) to the title compound using mercuric oxide (6.9 mmol, 1.5 g), triethylamine (20.7 mmol, 2.9 mL), and NH_3 (80 mL, 2 M solution in ethanol). This procedure afforded 600 mg (44%) of the title compound as a colorless solid, mp 109–113 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 6.17 (s, br, 2 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 3.80 (s, br, 2 H), 3.38 (d, *J* = 5.6 Hz, 2 H), 2.38 (s, 3 H), 1.65 (s, 3 H), 1.10 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.1, 141.8, 141.4, 139.9, 129.2, 126.0, 112.5, 53.3, 43.6, 21.6, 19.9, 12.9; IR (neat) 3424.3, 3337.1, 1633.8, 1557.3, 1489.9 cm^{-1}; MS (ESI+) 296.1430 (296.1427 calcd for $C_{14}H_{21}N_3O_2S$, M + H^+).



***N*-{[Allyl(phenethyl)amino](amino)methylene}-4-methylbenzenesulfonamide:**

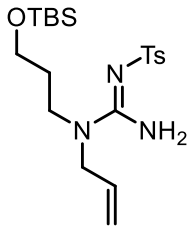
General procedure 2 was used for the conversion of methyl-*N*-allyl-*N*-phenethyl-*N*'-tosylcarbamimidothioate (5.0 mmol, 1.96 g) to the title compound using mercuric oxide

(7.6 mmol, 1.7 g), triethylamine (22.7 mmol, 3.2 mL), and NH_3 (75 mL, 2 M solution in ethanol). This procedure afforded 1.5 g (82%) of the title compound as a colorless solid, mp 89–91 °C: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.23–7.26 (m, 4 H), 7.19–7.22 (m, 1 H), 7.07 (d, *J* = 7.2 Hz, 2 H), 6.05 (s, br, 2 H), 5.60–5.67 (m, 1 H), 5.18 (d, *J* = 10.4 Hz, 1 H), 5.11 (d, *J* = 17.2 Hz, 1 H), 3.74 (s, br, 2 H), 3.55 (s, br, 2 H), 2.81 (t, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.0, 141.9, 141.4, 138.5, 132.2, 129.3, 128.9, 126.9, 126.1, 117.9, 51.5, 50.1, 34.6, 21.6, one peak is missing due to incidental equivalence; IR (neat) 3415.3, 3337.3, 1634.4, 1540.6, 1491.4, 1253.8 cm^{-1}; MS (ESI+) 358.1585 (358.1584 calcd for $C_{19}H_{23}N_3O_2S$, M + H^+).

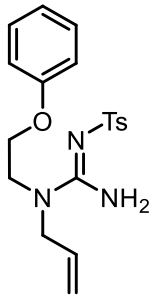


***N*-({[2-(1,3-Dioxan-2-yl)ethyl](allyl)amino}(amino)methylene)-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl-*N*-[2-(1,3-dioxan-2-yl)ethyl]-*N*-allyl-*N*'-tosylcarbamimidothioate (5.27 mmol, 2.1 g) to the title compound using mercuric oxide (7.9 mmol, 1.7 g), triethylamine (23.7 mmol, 3.3 mL), and NH_3 (80 mL, 2 M solution in ethanol). This procedure afforded 1.77 g (92%) of the title compound as a viscous oil: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.74–7.77 (m, 2 H), 7.19–7.22 (m, 2 H), 6.39–6.77 (s, br, 2 H), 5.66–5.74 (m, 1 H), 5.12 (d, *J* = 9.9 Hz, 1 H), 5.08 (d, *J* = 17.2 Hz, 1 H), 4.53 (t, *J* = 4.8 Hz, 1 H), 4.01–4.06 (m, 2 H), 3.97 (s, br, 2 H), 3.68 (td, *J* = 12.3, 2.4 Hz, 2 H), 3.33 (s, br, 2 H), 2.37 (s, 3 H), 1.97–2.05 (m,

1 H), 1.81 (td, *J* = 6.7, 4.9 Hz, 2 H), 1.33 (d, *J* = 13.6 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.1, 141.7, 141.5, 132.9, 129.2, 126.1, 117.9, 99.5, 66.9, 50.7, 41.6, 33.3, 25.6, 21.6; IR (neat) 3417.9, 3337.1, 2959.8, 1630.8, 1544.6, 1487.8, 1259.0 cm^{-1}; MS (ESI+) 368.1640 (368.1639 calcd for $C_{17}H_{25}N_3O_4S$, M + H^+).

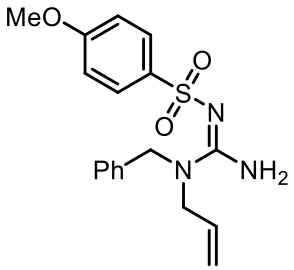


***N*-[(allyl{3-[(*tert*-butyldimethylsilyl)oxy]propyl}amino)(amino)methylene]-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl-*N*-allyl-*N*-{3-[(*tert*-butyldimethylsilyl)oxy]propyl}-*N*'-tosylcarbamimidothioate (5.2 mmol, 2.4 g) to the title compound using mercuric oxide (7.8 mmol, 1.7 g), triethylamine (23.4 mmol, 3.3 mL), and NH_3 (75 mL, 2 M solution in ethanol). This procedure afforded 1.2 g (54%) of the title compound as a colorless solid, mp 89–92 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.78 (s, br, 2 H), 5.68–5.77 (m, 1 H), 5.04–5.15 (m, 2 H), 3.97 (d, *J* = 5.6 Hz, 2 H), 3.59 (t, *J* = 5.5 Hz, 2 H), 3.33 (t, *J* = 5.9 Hz, 2 H), 2.38 (s, 3 H), 1.64–1.73 (m, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H), one peak is missing due to incidental equivalence; ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 141.7, 141.6, 133.2, 129.2, 126.1, 117.8, 59.1, 50.7, 30.5, 26.0, 21.6, 18.4, -5.2; IR (neat) 3421.2, 3339.8, 2927.4, 1630.3, 1543.0, 1487.7, 1256.8 cm^{-1}; MS (ESI+) 426.2241 (426.2241 calcd for $C_{20}H_{35}N_3O_3SSi$, M + H^+).



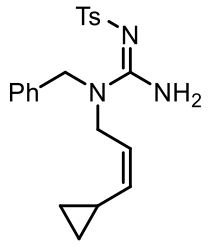
***N*-{[allyl(2-phenoxyethyl)amino](amino)methylene}-4-methylbenzenesulfonamide:**

General procedure 2 was used for the conversion of methyl-*N*-allyl-*N*-(2-phenoxyethyl)-*N*'-tosylcarbamimidothioate (5.0 mmol, 2.0 g) to the title compound using mercuric oxide (7.5 mmol, 1.6 g), triethylamine (22.5 mmol, 3.2 mL), and NH_3 (75 mL, 2 M solution in ethanol). This procedure afforded 1.1 g (59%) of the title compound as a colorless solid, mp 100–105 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2 H), 7.24–7.30 (m, 2 H), 7.21 (d, J = 8.1 Hz, 2 H), 6.98 (t, J = 7.3 Hz, 1 H), 6.79 (d, J = 7.8 Hz, 2 H), 6.51 (s, br, 2 H), 5.75–5.85 (m, 1 H), 5.12–5.24 (m, 2 H), 4.01–4.12 (m, 4 H), 3.73 (s, br, 2 H), 2.38 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.0, 157.0 142.0, 141.3, 132.7, 129.8, 129.3, 126.1, 121.7, 118.1, 114.5, 67.1, 52.3, 48.6, 21.6; IR (neat) 3416.0, 3327.7, 1626.6, 1544.5, 1489.5, 1259.9 cm^{-1}; MS (ESI+) 375.1532 (375.1533 calcd for $C_{19}H_{23}N_3O_3S$, M + H^+).



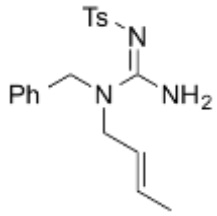
***N*-{[Allyl(benzyl)amino](amino)methylene}-4-methoxybenzenesulfonamide (2-7):**

General procedure 2 was used for the conversion of methyl *N*-allyl-*N*-benzyl-*N′*-[(4-methoxyphenyl)sulfonyl]carbamimidothioate (2.74 mmol, 1.07 g) to the title compound using mercuric oxide (4.1 mmol, 890 mg), triethylamine (12.0 mmol, 1.7 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 890 mg (90%) of the title compound as a colorless solid, mp 108–111 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.82 (m, 2 H), 7.23–7.29 (m, 3 H), 7.09–7.14 (m, 2 H), 6.87–6.91 (m, 2 H), 6.25 (s, br, 2 H), 5.63–5.74 (m, 1 H), 5.19 (dd, *J* = 10.3, 0.7 Hz, 1 H), 5.10–5.16 (m, 1 H), 4.57 (s, 2 H), 3.90 (s, br, 2 H), 3.84 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.0, 156.4, 136.2, 132.0, 129.0, 128.1, 128.0, 127.5, 118.1, 113.8, 55.7, 51.3, 50.4, one peak is missing due to incidental equivalence; IR (neat) 3417.5, 3320.8, 1613.4, 1541.0, 1488.0, 1249.5 cm^{-1}; MS (ESI+) 360.1381 (360.1376 calcd for $C_{18}H_{21}N_3O_3S$, M + H^+).



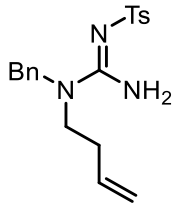
(Z)-*N*-{Amino[benzyl(3-cyclopropylallyl)amino]methylene}-4-methylbenzenesulfonamide: General procedure 2 was used for the conversion of (*2Z*)-Methyl *N*-benzyl-*N*-(-3-cyclopropylallyl)-*N′*-tosylcarbamimidothioate (2.4 mmol, 1.0 g) to the title compound using mercuric oxide (3.6 mmol, 780 mg), triethylamine (10.8 mmol, 1.5 mL), and NH_3 (50 mL, 2 M solution in ethanol). This procedure afforded 702 mg (76%) of the title compound as a colorless solid. The compound was isolated as a 1:3 mixture of *E:Z* alkene stereoisomers as determined by ^{1}H NMR analysis, mp 85–88

°C, ^{1}H NMR data are for the major isomer. ^{13}C NMR data are for the mixture of isomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.77 (m, 2 H), 7.21–7.27 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.11 (dd, *J* = 6.3, 2.7 Hz, 2 H), 6.17–6.35 (m, 2 H), 5.14 (dt, *J* = 10.6, 6.6 Hz, 1 H), 4.91 (t, *J* = 10.5 Hz, 1 H), 4.60 (s, 1 H), 4.02 (d, *J* = 4.7 Hz, 2 H), 2.38 (s, 3 H), 1.34–1.45 (m, 1 H), 0.69–0.77 (m, 2 H), 0.30–0.37 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.4, 141.8, 141.3, 139.1, 138.7, 129.2, 129.2, 128.9, 127.9, 127.6, 126.1, 121.5, 51.5, 45.4, 21.6, 13.5, 9.6, 7.4, 7.0; IR (neat) 3403.5, 3322.3, 1632.9, 1540.2, 1481.7, 1262.6 cm^{-1}; MS (ESI+) 384.1745 (384.1740 calcd for $C_{21}H_{25}N_3O_2S$, M + H^+).



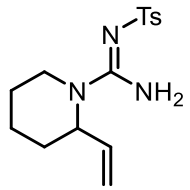
(2*E*)-*N*-(Amino[benzyl(but-2-en-1-yl)amino]methylene}-4-methylbenzenesulfonamide: General procedure 2 was used for the conversion of (*E)*-Methyl *N*-benzyl-*N*-(-but-2-en-1-yl)-*N′*-tosylcarbamimidothioate (2.5 mmol, 990 mg) to the title compound using mercuric oxide (3.8 mmol, 810 mg), triethylamine (11.3 mmol, 1.6 mL), and NH_3 (50 mL, 2 M solution in ethanol). This procedure afforded 760 mg (85%) of the title compound as a colorless solid. The compound was isolated as an 85:15 mixture of *E:Z* alkene stereoisomers as determined by ^{1}H NMR analysis, mp 61–68 °C; ^{1}H NMR data are for the major isomer. ^{13}C NMR data are for the mixture of isomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2 H), 7.14–7.28 (m, 5 H), 7.03–7.12 (m, 2 H), 6.22 (s, br, 2 H), 5.49–5.61 (m, 1 H), 5.21–5.34 (m, 1 H), 4.55 (s, 2 H), 3.80 (s, br, 2 H), 2.38 (s, 3 H), 1.64 (d, *J* = 6.3 Hz, 5 H); ^{13}C NMR (175 MHz, $CDCl_3$)

δ 156.4, 156.4, 141.9, 141.8, 141.3, 141.3, 129.9, 129.2, 129.2, 129.2, 128.9, 128.9, 127.9, 127.9, 127.5, 126.1, 124.8, 124.7, 51.2, 49.9, 44.9, 21.6, 17.8, 13.1; IR (neat) 3428.1, 3336.7, 1625.9, 1537.3, 1486.5, 1251.5 cm^{-1}; MS (ESI+) 358.1587 (358.1584 calcd for $C_{19}H_{23}N_3O_2S$, M + H^+).

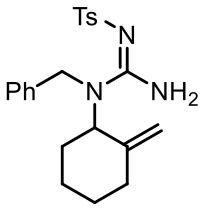


***N*-{Amino[benzyl(but-3-en-1-yl)amino]methylene}-4-methylbenzenesulfonamide:**

General procedure 2 was used for the conversion of methyl-*N*-benzyl-*N*-(but-3-en-1-yl)-*N*'-tosylcarbamimidothioate (3.3 mmol, 1.28 g) to the title compound using mercuric oxide (4.9 mmol, 1.0 g), triethylamine (14.9 mmol, 2.0 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 840 mg (71%) of the title compound as a colorless solid, mp 121–123 °C: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2 H), 7.26–7.30 (m, 3 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.09–7.12 (m, 2 H), 6.22 (s, br, 2 H), 5.69 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1 H), 4.98–5.04 (m, 2 H), 4.54 (s, br, 2 H), 3.41 (s, br, 2 H), 2.40 (s, 3 H), 2.27 (q, *J* = 7.2 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.1, 141.9, 141.3, 135.9, 134.5, 129.2, 129.1, 128.1, 127.0, 126.1, 117.9, 51.6, 48.2, 32.3, 21.6; IR (neat) 3413.1, 3317.9, 1618.3, 1541.7, 1489.5, 1247.0 cm^{-1}; MS (ESI+) 358.1585 (358.1584 calcd for $C_{19}H_{23}N_3O_2S$, M + H^+).

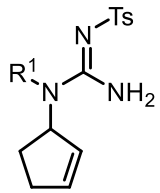


***N′*-Tosyl-2-vinylpiperidine-1-carboximidamide (2-30):** General procedure 2 was used for the conversion of methyl *N*-tosyl-2-vinylpiperidine-1-carbimidothioate (3.2 mmol, 1.08 g) to the title compound using mercuric oxide (4.8 mmol, 1.0 g), triethylamine (14.4 mmol, 2.0 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 630 mg (64%) of the title compound as a colorless solid. mp 115–119 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 2 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.27 (s, br, 2 H), 5.67 (ddd, *J* = 17.4, 10.6, 4.0 Hz, 1 H), 5.16 (dd, *J* = 10.6, 1.6 Hz, 1 H), 4.89–4.95 (m, 1 H), 4.84 (s, br, 1 H), 3.95 (d, *J* = 13.2 Hz, 1 H), 2.93 (td, *J* = 12.8, 3.3 Hz, 1 H), 2.38 (s, 3 H), 1.56–1.82 (m, 4 H), 1.39–1.54 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.0, 141.8, 141.3, 135.6, 129.2, 126.1, 116.9, 53.7, 40.7, 29.0, 25.0, 21.6, 19.0; IR (neat) 3417.0, 3337.1, 1634.2, 1520.6, 1480.7, 1256.1 cm^{-1}; MS (ESI+) 308.1430 (308.1427 calcd for $C_{15}H_{21}N_3O_2S$, M + H^+).

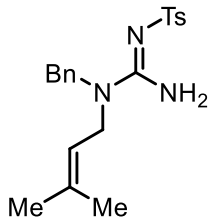


***N*-{Amino[benzyl(2-methylenecyclohexyl)amino]methylene}-4-methylbenzenesulfonamide (2-32):** General procedure 2 was used for the conversion of methyl *N*-benzyl-*N*-(2-methylenecyclohexyl)-*N′*-tosylcarbamimidothioate (3.0 mmol, 1.3 g) to the title compound using mercuric oxide (4.8 mmol, 1.0 g), triethylamine (13.5

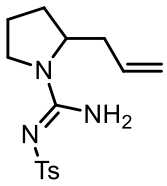
mmol, 1.9 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 320 mg (27%) of the title compound as a colorless solid: mp 76–80 °C. The product was determined to exist as a mixture of conformers as judged by ^{1}H NMR analysis. ^{1}H NMR data are for the major conformer, whereas ^{13}C NMR data are for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2 H), 7.08–7.29 (m, 7 H), 6.15 (s, br, 2 H), 4.77 (s, br, 2 H), 4.34–4.47 (m, 2 H), 2.32–2.47 (m, 4 H), 2.07 (t, *J* = 12.5 Hz, 1 H), 1.75 (s, br, 3 H), 1.41 (s, br, 2 H), 1.08–1.28 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.1, 145.4, 141.8, 141.2, 129.1, 128.9, 127.6, 126.5, 126.2, 107.1, 60.5, 48.9, 35.0, 31.9, 26.9, 25.7, 22.8, 21.6; IR (neat) 3427.0, 3328.2, 2933.9, 1625.0, 1516.7, 1487.8 cm^{-1}; MS (ESI+) 398.1900 (398.1897 calcd for $C_{22}H_{27}N_3O_2S$, M + H^+).



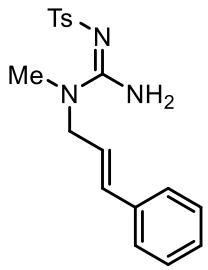
***N*-(Amino(benzyl(cyclopent-2-en-1-yl)amino)methylene)-4-methylbenzenesulfonamide (2-23):** General procedure 2 was used for the conversion of methyl-*N*-benzyl-*N*-(cyclopent-2-en-1-yl)-*N*'-tosylcarbamimidothioate (2.82 mmol, 1.13 g) to the title compound using mercuric oxide (4.2 mmol, 910 mg), triethylamine (12.7 mmol, 1.8 mL), and NH_3 (60 mL, 2 M solution in ethanol). This procedure afforded 620 mg (60%) of the title compound as a colorless solid: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.24–7.31 (m, 3 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 7.12 (d, *J* = 7.3 Hz, 2H), 6.12 (br. s, 2 H), 5.95–5.99 (m, 1 H), 5.56–5.61 (m, 1 H), 4.33–4.51 (m, 2 H), 2.40 (s, 3 H), 2.26–2.33 (m, 2 H), 1.60 (s, 1 H).



***N*-(Amino(benzyl(3-methylbut-2-en-1-yl)amino)methylene)-4-methylbenzenesulfonamide:** General procedure 2 was used for the conversion of methyl-*N*-benzyl-*N*-(3-methylbut-2-en-1-yl)-*N*'-tosylcarbamimidothioate (2.8 mmol, 1.13 g) to the title compound using mercuric oxide (4.2 mmol, 900 mg), triethylamine (12.6 mmol, 1.8 mL), and NH_3 (50 mL, 2 M solution in ethanol). This procedure afforded 1.0 g (96%) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2 H), 7.31–7.20 (m, 5H), 7.13 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.15 (s, 2H), 5.06 (t, *J* = 7.0 Hz, 1 H), 4.57 (s, 2 H), 3.87 (d, *J* = 6.6 Hz, 2 H), 2.40 (s, 3 H), 1.70 (s, 3 H), 1.60 (s, 3 H).



2-Allyl-*N*'-tosylpyrrolidine-1-carboximidamide (2-21): General procedure 2 was used for the conversion of methyl-2-allyl-N-tosylpyrrolidine-1-carbimidothioate (3.4 mmol, 1.16 g) to the title compound using mercuric oxide (5.1 mmol, 1.1 g), triethylamine (15.3 mmol, 2.13 mL), and NH_3 (70 mL, 2 M solution in ethanol). This procedure afforded 750 mg (72%) of the title compound as a colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 2 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 6.02 (s, br, 2 H), 5.62–5.70 (m, 1 H), 4.95–5.99 (m, 2 H), 4.14 (br. s, 1 H), 2.39–2.44 (br. s, 2 H), 2.05–2.11 (m, 1 H), 1.89–1.91 (m, 3 H), 1.82–1.83 (m, 1 H)



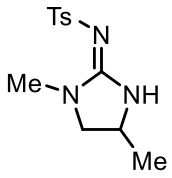
***N*-(Amino(cinnamyl(methyl)amino)methylene)-4-methylbenzenesulfonamide:**

General procedure 2 was used for the conversion of methyl-*N*-benzyl-*N*-cinnamyl-*N*'-tosylcarbamimidothioate (2.9 mmol, 1.08 g) to the title compound using mercuric oxide (4.4 mmol, 942 mg), triethylamine (12.8 mmol, 1.8 mL), and NH_3 (40 mL, 2 M solution in ethanol). This procedure afforded 620 mg (62%) of the title compound as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 2 H), 7.27–7.36 (m, 4 H), 7.21 (d, J = 8.0 Hz, 2 H), 6.40 (d, J = 15.9 Hz, 1 H), 6.18 (s, 2 H), 6.06 (dt, J = 15.9, 5.9 Hz, 1 H), 4.15 (d, J = 6.0 Hz, 2 H), 2.98 (s, 3 H), 2.38 (s, 3 H).

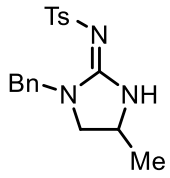
General Procedure 3 for intramolecular Ag-catalyzed guanidine hydroamination reactions:

An oven-dried test tube was charged with the appropriate guanidine substrate (1.0 equiv), sodium *tert*-butoxide (1.0 equiv), and 15-40 mol% silver nitrate. The tube was capped with a septum and purged with oxygen. Chlorobenzene (0.1 M) was added, and a balloon of oxygen was affixed to the septum with a needle connection. The mixture was stirred vigorously at room temperature for 10 min, and then transferred to a hotplate and heated to (80–100 °C) with vigorous stirring until the starting material had been completely consumed (16–24 h). The mixture was then cooled to rt and the

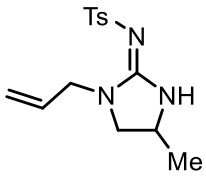
reaction was quenched with saturated ammonium chloride (8 mL/mmol). The mixture was transferred to a separatory funnel and the aqueous layer was extracted with ethyl acetate (3 x 8 mL/mmol). The combined organic layers were filtered through a plug of celite, and solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using dichloromethane/methanol as eluant.



***N*-(1,4-Dimethylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-6):** General procedure 3 was used for the hydroamination of *N*-{[Allyl(methyl)amino](amino)methylene}-4-methylbenzenesulfonamide (0.25 mmol, 67 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 16 h at 80°C. This procedure afforded 63 mg (94%) of the title compound as a colorless solid, mp 175–177 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.95 (s, br, 1 H), 3.89–4.00 (m, 1 H), 3.53 (t, *J* = 9.1 Hz, 1 H), 2.98 (dd, *J* = 9.2, 7.2 Hz, 1 H), 2.82 (s, 3 H), 2.37 (s, 3 H), 1.25 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.5, 141.9, 141.1, 129.2, 126.2, 54.9, 48.7, 31.4, 21.6, 21.2; IR (neat) 3375.2, 2917.5, 1586.1, 1531.5, 1256.5 cm^{-1}; MS (ESI+) 268.1120 (268.1114 calcd for $C_{12}H_{17}N_3O_2S$, M + H^+).

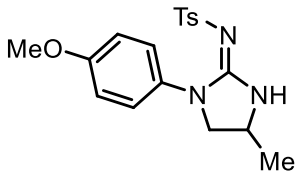


***N*-(1-Benzyl-4-methylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-10):** General procedure 3 was used for the hydroamination of *N*-{[Allyl(benzyl)amino](amino)methylene}-4-methylbenzenesulfonamide (0.25 mmol, 90 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 16 h at 80°C. This procedure afforded 89 mg (90%) of the title compound as a colorless solid, mp 104–105 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2 H), 7.23–7.28 (m, 5 H), 7.12 (dd, *J* = 6.6, 2.8 Hz, 2 H), 7.07 (s, br, 1 H), 4.39–4.49 (m, 2 H), 3.88–3.99 (m, 1 H), 3.41 (t, *J* = 9.2 Hz, 1 H), 2.86 (dd, *J* = 9.2, 7.0 Hz, 1 H), 2.41 (s, 3 H), 1.22 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.1, 142.0, 141.1, 135.8, 129.2, 128.8, 128.2, 127.9, 126.2, 51.8, 48.8, 48.0, 21.6, 21.2 ; IR (neat) 3381.9, 1578.0, 1508.6, 1260.0 cm^{-1}; MS (ESI+) 344.1432 (344.1427 calcd for $C_{18}H_{21}N_3O_2S$, M + H^+).



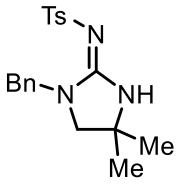
***N*-(1-Allyl-4-methylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-11):** General procedure 3 was used for the hydroamination of *N*-[Amino(diallylamino)methylene]-4-methylbenzenesulfonamide (0.25 mmol, 74 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at

80°C. This procedure afforded 69 mg (94%) of the title compound as a colorless solid, mp 99–103 °C: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 6.99 (s, br, 1 H), 5.64 (ddt, *J* = 16.9, 10.4, 6.1 Hz, 1 H), 5.15 (dd, *J* = 10.2, 1.2 Hz, 1 H), 5.10–5.13 (m, 1 H), 3.91–3.97 (m, 1 H), 3.80–3.89 (m, 2 H), 3.49 (t, *J* = 9.2 Hz, 1 H), 2.94 (dd, *J* = 9.4, 7.2 Hz, 1 H), 2.37 (s, 3 H), 1.25 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.0, 142.0, 141.0, 132.1, 129.2, 126.2, 118.7, 52.0, 48.8, 46.9, 21.6, 21.2; IR (neat) 3347.3, 2915.7, 1576.2, 1514.2, 1264.2 cm^{-1}; MS (ESI+) 294.1277 (294.1271calcd for $C_{14}H_{19}N_3O_2S$, M + H^+).

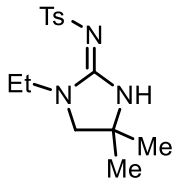


***N*-[1-(4-Methoxyphenyl)-4-methylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide (2-12):** General procedure 3 was used for the hydroamination of *N*-{[Allyl(4-methoxyphenyl)amino](amino)methylene}-4-methylbenzenesulfonamide (0.25 mmol, 90 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 16 h at 80°C. This procedure afforded 89 mg (99%) of the title compound as a colorless solid, mp 111–113 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2 H), 7.35 (s, 1 H), 7.27–7.32 (m, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 6.79–6.85 (m, 2 H), 4.02–4.12 (m, 1 H), 3.92–3.99 (m, 1 H), 3.77 (s, 3 H), 3.44 (dd, *J* = 9.0, 7.0 Hz, 1 H), 2.38 (s, 3 H), 1.34 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.0, 156.2, 142.1, 140.8, 131.6, 129.3, 126.2, 123.4, 114.2, 55.6, 54.6, 48.4, 21.6, 21.2; IR (neat) 3370.0, 1569.0, 1512.4, 1246.7 cm^{-1}; MS (ESI+)

360.1380 (360.1376 calcd for $C_{18}H_{21}N_3O_3S$, M + H^+).

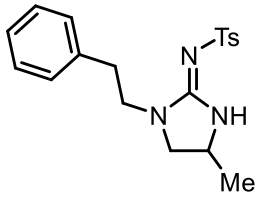


***N*-(1-Benzyl-4,4-dimethylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-13):** General procedure 3 was used for the hydroamination of *N*-{Amino[benzyl(2-methylallyl)amino]methylene}-4-methylbenzenesulfonamide (0.25 mmol, 90 mg) with $AgNO_3$ (0.05 mmol, 8.5 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at 100°C. This procedure afforded 85 mg (94%) of the title compound as a colorless solid, mp 130–133 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2 H), 7.22–7.27 (m, 5 H), 7.08–7.13 (m, 2 H), 6.98 (s, 1 H), 4.44 (s, 2 H), 3.03 (s, 2 H), 2.41 (s, 3 H), 1.28 (s, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.2, 142.0, 141.2, 135.9, 129.3, 128.8, 128.2, 127.9, 126.2, 57.5, 56.1, 48.0, 28.3, 21.6; IR (neat) 3343.8, 1579.0, 1508.2, 1266.8 cm^{-1}; MS (ESI+) 358.1590 (358.1584 calcd for $C_{19}H_{23}N_3O_2S$, M + H^+).

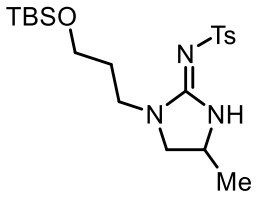


***N*-(1-Ethyl-4,4-dimethylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-14):** General procedure 3 was used for the hydroamination of *N*-{Amino[ethyl(2-methylallyl)amino]methylene}-4-methylbenzenesulfonamide (0.25 mmol, 90 mg) with $AgNO_3$ (0.05 mmol, 8.5 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at

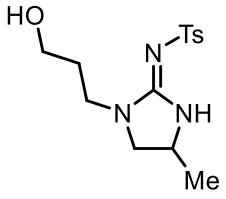
100°C. This procedure afforded 71 mg (96%) of the title compound as a colorless solid, mp 168–173 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.77 (m, 2 H), 7.18–7.22 (m, 2 H), 6.89 (s, br, 1 H), 3.29 (q, *J* = 7.1 Hz, 2 H), 3.14 (s, 2 H), 2.36 (s, 3 H), 1.28 (s, 6 H), 1.03 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.0, 141.8, 141.3, 129.2, 126.0, 57.5, 55.9, 38.7, 28.1, 21.5, 12.4; IR (neat) 3342.1, 2920.0, 1581.7, 1514.8, 1259.9 cm^{-1}; MS (ESI+) 296.1435 (296.1427 calcd for $C_{14}H_{21}N_3O_2S$, M + H^+).



4-Methyl-*N*-(4-methyl-1-phenethylimidazolidin-2-ylidene)benzenesulfonamide (2-15): General procedure 3 was used for the hydroamination of *N*-{[Allyl(phenethyl)amino](amino)methylene}-4-methylbenzenesulfonamide (0.25 mmol, 89 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at 80°C. This procedure afforded 87 mg (98%) of the title compound as a colorless solid, mp 114–118 °C: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76–7.79 (m, 2 H), 7.20–7.25 (m, 4 H), 7.16–7.20 (m, 1 H), 7.07–7.10 (m, 2 H), 6.92 (s, 1 H), 3.81–3.87 (m, 1 H), 3.50–3.53 (m, 2 H), 3.35 (t, *J* = 9.2 Hz, 1 H), 2.75–2.83 (m, 3 H), 2.40 (s, 3 H), 1.14 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.0, 142.0, 141.2, 138.6, 129.3, 128.9, 128.7, 126.7, 126.2, 53.1, 48.8, 45.4, 34.0, 21.6, 21.2; IR (neat) 3349.6, 2925.8, 1576.3, 1266.2, 1128.8 cm^{-1}; MS (ESI+) 358.1586 (358.1584 calcd for $C_{19}H_{23}N_3O_2S$, M + H^+).

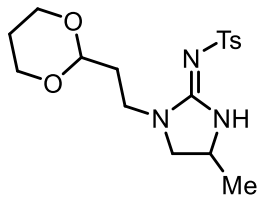


***N*-(1-{3-[(*tert*-Butyldimethylsilyl)oxy]propyl}-4-methylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-16):** General procedure 3 was used for the hydroamination of *N*-[(allyl{3-[(*tert*-butyldimethylsilyl)oxy]propyl}amino)(amino)methylene]-4-methylbenzenesulfonamide (0.25 mmol, 106 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at 80°C. This procedure afforded 74 mg (70%) of the title compound as a colorless solid, mp 84–87 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 6.94 (s, br, 1 H), 3.90–3.98 (m, 1 H), 3.54–3.59 (m, 3 H), 3.25–3.38 (m, 2 H), 3.01 (dd, *J* = 9.0, 7.1 Hz, 1 H), 2.37 (s, 3 H), 1.63–1.71 (m, 2 H), 1.24 (d, *J* = 6.1 Hz, 3 H), 0.85 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.2, 141.8, 141.2, 129.2, 126.1, 60.5, 52.9, 48.8, 41.4, 30.6, 26.0, 21.6, 21.2, 18.4, -5.3; IR (neat) 3353.0, 2926.4, 2856.6, 1581.7, 1515.8, 1262.4, 1084.3 cm^{-1}; MS (ESI+) 426.2243 (426.2241 calcd for $C_{20}H_{35}N_3O_3SSi$, M + H$^+$).



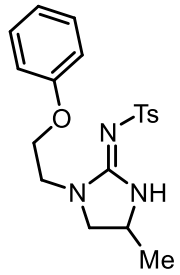
***N*-[1-(3-Hydroxypropyl)-4-methylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide**: The hydroamination of substrate **2-16** generated approximately 20% of de-silylated cyclic guanidine *N*-[1-(3-Hydroxypropyl)-4-

methylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide. The identity of *N*-[1-(3-Hydroxypropyl)-4-methylimidazolidin-2-ylidene]-4-methylbenzenesulfonamide was verified by TBAF deprotection of **2-16**. A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with **2-16** (104 mg, 0.25 mmol) and THF (2.5 mL). The mixture was cooled to 0 °C then a solution of TBAF (300 µL, 1 M solution in THF) was then added dropwise. The resulting mixture was stirred at rt for 80 minutes, then a solution of saturated ammonium chloride (2 mL) was added, the mixture was transferred to a separatory funnel and the aqueous layer was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were filtered through a plug of celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using dichloromethane/methanol as eluant. This afforded 39 mg (50 %) of the title compound as a colorless solid, mp 114–117 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (*J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 6.97 (s, 1 H), 3.95–4.04 (m, 1 H), 3.58 (t, *J* = 9.3 Hz, 1 H), 3.43–3.52 (m, 2 H), 3.33–3.43 (m, 2 H), 3.05 (dd, *J* = 9.4, 7.0 Hz, 1 H), 2.98 (s, br, 1 H), 2.38 (s, 3 H), 1.60–1.68 (m, 2 H), 1.28 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.49, 142.36, 140.53, 129.38, 126.23, 58.20, 52.74, 49.05, 40.39, 29.75, 21.33; IR (neat) 3374.6, 2943.3, 1585.0, 1526.1, 1259.6 cm^{-1}; MS (ESI+) 312.1376 (312.1375 calcd for $C_{14}H_{21}N_3O_3S$, M + H^+).



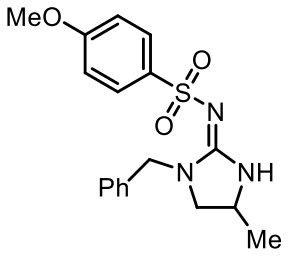
***N*-{1-[2-(1,3-Dioxan-2-yl)ethyl]-4-methylimidazolidin-2-ylidene}-4-**

methylbenzenesulfonamide (2-17): General procedure 3 was used for the hydroamination of *N*-({[2-(1,3-Dioxan-2-yl)ethyl](allyl)amino}(amino)methylene)-4-methylbenzenesulfonamide (0.25 mmol, 92 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at 80°C. This procedure afforded 81 mg (88%) of the title compound as a colorless solid, mp 108–110 °C: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.91 (s, 1 H), 4.52 (t, *J* = 5.0 Hz, 1 H), 3.97–4.03 (m, 2 H), 3.90–3.96 (m, 1 H), 3.62 (dtd, *J* = 18.2, 12.0, 2.6 Hz, 2 H), 3.55 (t, *J* = 9.2 Hz, 1 H), 3.38 (t, *J* = 7.1 Hz, 2 H), 3.02 (dd, *J* = 9.2, 7.0 Hz, 1 H), 2.38 (s, 3 H), 1.96–2.04 (m, 1 H), 1.71–1.80 (m, 2 H), 1.23–1.29 (m, 4 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.2, 141.9, 141.3, 129.2, 126.2, 100.5, 66.9, 66.9, 52.5, 48.9, 39.7, 32.9, 25.8, 21.6, 21.3; IR (neat) 3350.6, 1575.8, 1262.4, 1127.8 cm^{-1}; MS (ESI+) 368.1638 (368.1639 calcd for $C_{17}H_{25}N_3O_4S$, M + H^+).

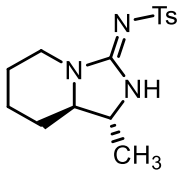


4-Methyl-*N*-[4-methyl-1-(2-pheno5xyethyl)imidazolidin-2-ylidene]benzenesulfonamide (2-18): General procedure 3 was used for the hydroamination of *N*-{[allyl(2-phenoxyethyl)amino](amino)methylene}-4-methylbenzenesulfonamide (0.25 mmol, 93 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 18 h at 80°C. This procedure afforded 84 mg (90%) of the title compound as a colorless solid, mp 127–129 °C: ^{1}H NMR (500

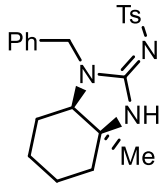
MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2 H), 7.18–7.31 (m, 4 H), 6.90–7.02 (m, 2 H), 6.79 (d, *J* = 7.8 Hz, 2 H), 3.99–4.13 (m, 2 H), 3.89–3.99 (m, 1 H), 3.78 (t, *J* = 9.2 Hz, 1 H), 3.65–3.72 (m, 1 H), 3.58–3.65 (m, 1 H), 3.22 (dd, *J* = 9.2, 7.2 Hz, 1 H), 2.38 (s, 3 H), 1.24 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.4, 158.2, 142.0, 141.1, 129.7, 129.3, 126.2, 121.3, 114.5, 66.8, 54.3, 49.1, 44.0, 21.6, 21.2; IR (neat) 3360.0, 1576.1, 1506.5, 1243.6 cm^{-1}; MS (ESI+) 374.1536 (374.1533 calcd for $C_{19}H_{23}N_3O_3S$, M + H^+).



***N*-(1-benzyl-4-methylimidazolidin-2-ylidene)-4-methoxybenzenesulfonamide (2-8):** General procedure 3 was used for the hydroamination of **2-7** (0.25 mmol, 90 mg) with $AgNO_3$ (0.038 mmol, 6.4 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg). The reaction was conducted for 18 h at 80°C. This procedure afforded 85 mg (94%) of the title compound as a colorless solid. mp 118–122 °C: ^1H NMR (500 MHz, $CDCl_3$) δ 7.82–7.87 (m, 2 H), 7.21–7.25 (m, 3 H), 7.10 (dt, *J* = 3.8, 2.8 Hz, 2 H), 7.05 (s, 1 H), 6.89–6.94 (m, 2 H), 4.38–4.46 (m, 2 H), 3.87–3.96 (m, 1 H), 3.83 (s, 3 H), 3.40 (t, *J* = 9.2 Hz, 1 H), 2.84 (dd, *J* = 9.3, 7.1 Hz, 1 H), 1.20 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.1, 158.0, 136.0, 135.8, 128.8, 128.2, 128.1, 127.9, 113.8, 55.6, 51.7, 48.8, 48.0, 21.2; IR (neat) 3370.1, 2916.0, 1565.8, 1517.0, 1500.6, 1252.8 cm^{-1}; MS (ESI+) 360.1379 (360.1376 calcd for $C_{18}H_{21}N_3O_3S$, M + H^+).

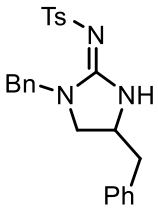


4-Methyl-*N*-(1-methylhexahydroimidazo[1,5-*a*]pyridin-3(2*H*)-ylidene)benzenesulfonamide (2-31): General procedure 3 was used for the hydroamination of **2-30** (0.25 mmol, 77 mg) with $AgNO_3$ (0.1 mmol, 17.0 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 24 h at 100°C. This procedure afforded 65 mg (84%) of the title compound as an colorless solid, mp 76–79 °C. This material was determined to be a 3:1 mixture of diastereomers as judged by ^{1}H NMR analysis. Data are for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.94 (s, br, 1 H), 3.88–4.02 (m, 1 H), 3.40–3.51 (m, 1 H), 2.95–3.02 (m, 1 H), 2.56–2.69 (m, 1 H), 2.36 (s, 3 H), 1.76–1.91 (m, 2 H), 1.52–1.64 (m, 2 H), 1.30–1.37 (m, 2 H), 1.23 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.9, 141.9, 141.2, 129.2, 126.2, 63.2, 55.9, 41.6, 29.9, 24.6, 23.2, 21.6, 19.7; IR (neat) 3375.5, 2934.7, 1567.3, 1494.7, 1254.8 cm^{-1}; MS (ESI+) 308.1435 (308.1427 calcd for $C_{15}H_{21}N_3O_2S$, M + H^+).



(3a*S*,7a*R*)-*N*-(1-Benzyl-3a-methyloctahydro-2*H*-benzo[*d*]imidazol-2-ylidene)-4-methylbenzenesulfonamide (2-33): General procedure 3 was used for the

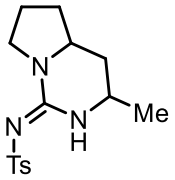
hydroamination of **2-32** (0.25 mmol, 99 mg) with $AgNO_3$ (0.1 mmol, 17.0 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) for 24 h at 100°C. This procedure afforded 98 mg (99%) of the title compound as a colorless solid. mp 153–156 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.16–7.22 (m, 3 H), 7.07 (d, *J* = 6.4 Hz, 2 H), 7.03 (s, 1 H), 4.93 (d, *J* = 15.4 Hz, 1 H), 3.97 (d, *J* = 15.2 Hz, 1 H), 3.01 (t, *J* = 4.3 Hz, 1 H), 2.41 (s, 3 H), 1.68–1.77 (m, 1 H), 1.56–1.61 (m, 2 H), 1.45–1.55 (m, 2 H), 1.30–1.38 (m, 1 H), 1.22–1.29 (m, 2 H), 1.21 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 158.5, 141.9, 141.2, 136.0, 129.2, 128.7, 128.2, 127.7, 126.2, 60.3, 58.0, 45.4, 35.0, 25.1, 23.3, 21.6, 20.6, 19.5 ; IR (neat) 3316.1, 2936.6, 1574.3, 1254.6 cm^{-1}; MS (ESI+) 397.1901 (398.1897 calcd for $C_{22}H_{27}N_3O_2S$, M + H^+).



***N*-(4-benzyl-1-methylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide**

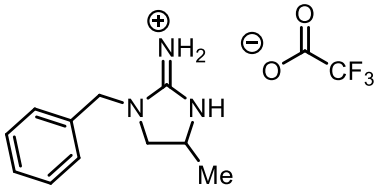
(Scheme 2.5, entry 4): General procedure 3 was used for the hydroamination of *N*-(amino(cinnamyl(methyl)amino)methylene)-4-methylbenzenesulfonamide (0.25 mmol, 86 mg) with $AgNO_3$ (0.05 mmol, 8.5 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) in PhCl (0.1 M) for 19 h at 100°C. This procedure afforded a 3:2 mixture of sm and desired product based on analysis of the crude reaction mixture. The assignment of the desired product was made on the basis of the following signals in the crude reaction mixture (*Note: not all of the signals are outlined following as the starting material and the product were inseparable by conventional chromatography*): ^{1}H NMR (400 MHz,

$CDCl_3$) δ 3.97–4.04 (m, 1 H), 3.44 (t, *J* = 9.2 Hz, 1 H), 3.12 (dd, *J* = 6.8, 2.8 Hz, 1 H).



4-methyl-*N*-(3-methylhexahydropyrrolo[1,2-c]pyrimidin-1(2H)-ylidene)benzenesulfonamide (2-22): General procedure 3 was used for the hydroamination of 2-allyl-*N*'-tosylpyrrolidine-1-carboximidamide (0.25 mmol, 77 mg) with $AgNO_3$ (0.25 mmol, 43.0 mg), and sodium *tert*-butoxide (0.25 mmol, 24.0 mg) in PhCl (0.1 M) for 22 h at 100°C. This procedure afforded a 1:0.83 mixture of sm and desired product based on analysis of the crude reaction mixture. The dr was judged to be 3:1 based on analysis of the ratio of the doublet signals corresponding to the new methyl group at 1.26 ppm and 1.21 ppm.

Deprotection of Hydroamination Product 2-8

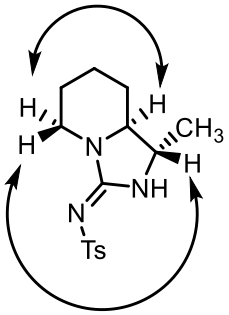


1-Benzyl-4-methylimidazolidin-2-iminium 2,2,2-trifluoroacetate (**2-36**): Hydroamination product **2-8** was deprotected using a procedure reported by Du Bois.[10] A round bottom flask was charged with hydroamination product **2-8** (55 mg, 0.15 mmol) and trifluoroacetic acid (9 mL). Neat methanesulfonic acid (0.45 mL, 7 mmol, 46 equiv)

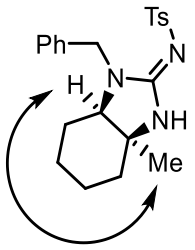
was added, followed by thioanisole (110 µL, 0.92 mmol, 6 equiv). The resulting mixture was stirred at rt for 28 h and then the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using dichloromethane/methanol as eluant. This procedure afforded 27 mg (60%) of the title compound as a colorless solid, mp 190–195 °C: ^{1}H NMR (700 MHz, CD_3OD) δ 7.42 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 4.09–4.01 (m, 1H), 3.70 (t, *J* = 9.4 Hz, 1H), 3.13 (dd, *J* = 9.7, 6.7 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H).; ^{13}C NMR (175 MHz, CD_3OD) δ 159.4, 135.8, 130.2, 129.4, 128.9, 55.3, 50.5, 20.8, one peak is missing due to incidental equivalence; IR (neat) 3162.8, 3041.6, 1667.7, 1560.2 cm^{-1}; MS (ESI+) 190.1340 (190.1339 calcd for $C_{11}H_{15}N_3$, M + H^+).

Assignment of Configuration

The configuration of **2-31** was assigned based on NOESY analysis as shown below.



The configuration of **2-33** was assigned based on NOESY analysis as shown below.



2.8 References

(1) For total syntheses of batzelladine alkaloids, see: (a) Snider, B.B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697; (b) Cohen, F.; Overman, L.E.; Sakata, S.K.L. *Org. Lett*. **1999**, *1*, 2169; (c) Cohen, F.; Overman, L.E. *J. Am. Chem. Soc*. **2006**, *128*, 2604; (d) Shimokawa, J.; Shirai, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Angew. Chem*. **2004**, *116*, 1585; *Angew. Chem. Int. Ed*. **2004**, *43*, 1559; (e) Arnold, M.A.; Day, K.A.; Durón, S.D.; Gin, D.Y. *J. Am. Chem. Soc*. **2006**, *128*, 13255; (f) Evans, P.A.; Qin, J.; Robinson, J.E.; Bazin, B. *Angew. Chem*. **2007**, *119*, 7561; *Angew. Chem. Int. Ed*. **2007**, *46*, 7417; (g) Parr, B.T.; Economou, C.; Herzon, S.B. *Nature*, **2015**, *525*, 507.

(2) (a) Babij, N. R.; Wolfe, J.P. *Angew. Chem*. **2012**, *124*, 4204; *Angew. Chem. Int. Ed*. **2012**, *51*, 4128; (b) Babij, N. R.; Wolfe, J.P. *Angew. Chem*. **2013**, *125*, 9417; *Angew. Chem. Int. Ed*. **2013**, *52*, 9247.

(3) Zavesky, B.P.; Babij, N.R.; Wolfe, J.P. *Org. Lett.* **2014**, *16*, 4952.

(4) Zavesky, B.P.; Babij, N.R.; Wolfe, J.P. *Org. Lett.* **2013**, *15*, 5420.

(5) (a) Fornwald, R.M.; Fritz, J.A.; Wolfe, J.P. *Chem. Eur. J.* **2014**, *20*, 8782; (b) Babij, N.R.; McKenna, G.M.; Fornwald, R.M.; Wolfe, J.P. *Org. Lett.* **2014**, *16*, 3412.

(6) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem*. **1985**, *50*, 3896.

(7) Silver Triflate has also been used in AgOTf-catalyzed Isomerization/Hydroalkoxylation Sequence for the synthesis of lactones. See Gooβen, L.J.; Ohlmann, D.M.; Dierker, M. *GreenChem*. **2010**, *12*, 197.

(8) For two different studies which demonstrate this, see: (a) Muhs, M.A.; Weiss, F.T. *J. Am. Chem. Soc.* **1962**, *84*, 4697; (b) Vardhan, H.B.; Bach, R.D. *J. Org. Chem*. **1985**, *50*, 3896.

(9) LaLonde, R.L. Brenzovich, Jr., W.E.; Tkatchouk, E.; Kelley, K.; Goddard, III, W.A.; Toste, F.D. *Chem Sci*. **2010**, *1*, 226.

(10) Fleming, J.J.; McReynolds, M.D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, 129, 9964.

(11) Ermolat'ev, D.S.; Bariwal, J.B.; Steenackers, H.P.L.; De Keersmaecker, S.C.J.; Van der Eycken, E.V. *Angew. Chem. Int. Ed*. **2010**, *49*, 9465.

(12) van Loevezijn, A.; Venhorst, J.; Iwema Bakker, W. I.; de Korte, C. G.; de Looff, W.; S. Verhoog, van Wees, J.-W.; van Hoeve, M.; van de Woestijne, R. P.; van der Neut, M. A. W.; Borst, A. J. M.; van Dongen, M. J. P.; de Bruin, N. M. W. J; Keizer, H. G.; Kruse, C. G. *J. Med. Chem.* **2011**, 54, 7030.

(13) Zavesky, B. P.; Babij, N. R.; Fritz, J. A.; Wolfe, J. P. *Org. Lett.*, **2013**, 15, 5420.

(14) Bosin, T. R.; Hanson, R. N.; Rodricks, J. V.; Simpson, R. A.; Rapoport, H. *J. Org. Chem.* **1973**, 38, 1591.

(15) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, 129, 11336.

(16) Betou, M.; Male, L.; Steed, J. W.; Grainger, R. S. *Chem. Eur. J*. **2014**, *20*, 6505.

(17) Marhold, M; Stillig, C.; Fröhlich, R.; Haufe, G. *Eur. J. Org. Chem*. **2014**, *26*, 5777.

(18) Trapella, C.; Fischetti, C.; Pela', M.; Lazzari, I.; Guerrini, R.; Calo', G.; Rizzi, A.; Camarda, V.; Lambert, D.G.; McDonald, J.; Regoli, D.; Salvadori, S. *Bioorg. Med. Chem.*, **2009**, *17*, 5080.

(19) Molander, G. A.; Nichols, P. J. *J. Org. Chem.*, **1996**, 61, 6040.

(20) Shivani; Pujala, B.; Chakraborti, A. K. *J. Org. Chem*. **2007**, *72*, 3713.

(21) Schuch, D.; Fries, P.; Dönges, M.; Menéndez Pérez, B.; Hartung, J. *J. Am. Chem. Soc.*, **2009**, 131, 12918.

(22) Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron*, **1998**, *54*, 6385.

(23) McCann, S.F.; Overman, L.E. *J. Am. Chem. Soc.* **1987**, 109, 6107.

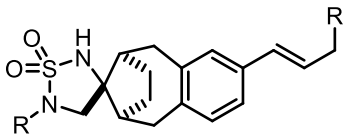
Chapter 3

Applications and Synthesis of Cyclic Sulfamides

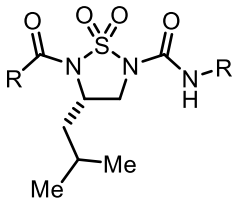
3.1 Background and Significance

Cyclic sulfamides are widely present in a number of biologically active compounds including natural products and pharmaceuticals.[1] In addition, the cyclic sulfamide motif has also been utilized as a chiral auxiliary in aldol reactions.[2] The sulfamide is a versatile functional group which can be readily cleaved[3] to produce important 1,2- and 1,3-diamines.[4] Examples of cyclic sulfamides are shown in **Figure 3.1** along with their specific function or use.

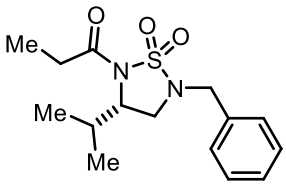
Figure 3.1 Examples of Cyclic Sulfamides



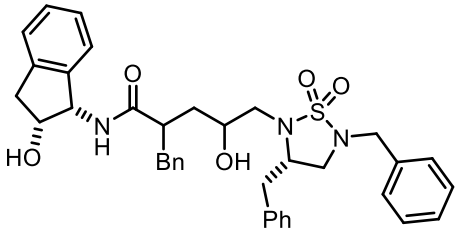
Gamma-Secretase Inhibitor



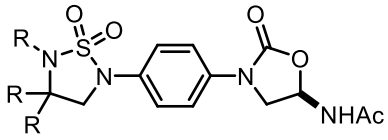
Enzyme Inhibitor



Chiral Auxiliary



HIV Protease Inhibitor



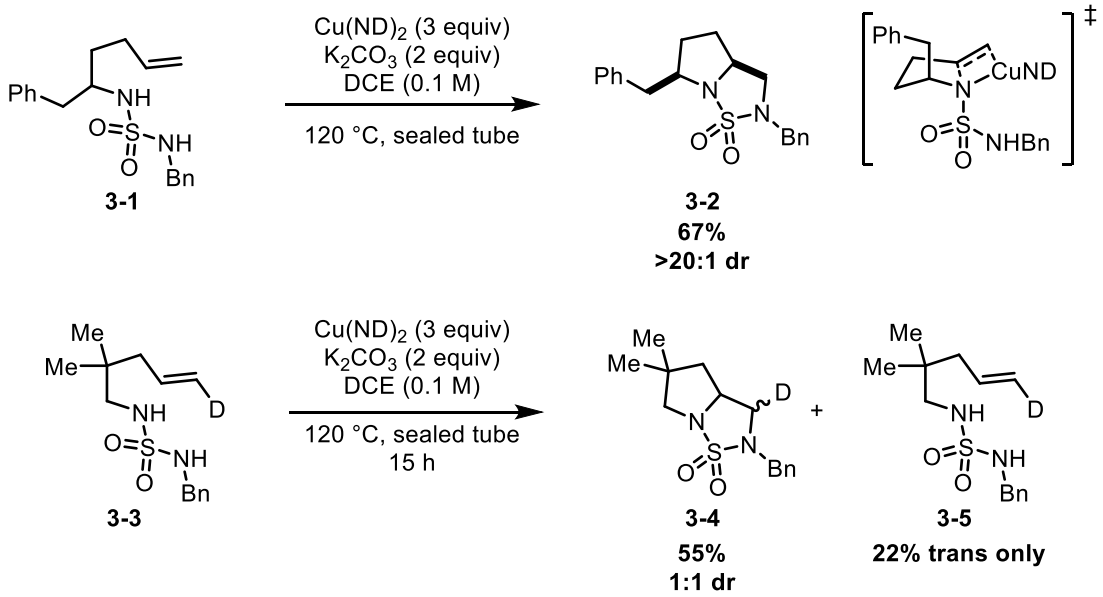
Antibacterial

Due to the prevalence of this moiety, several groups have devoted synthetic efforts towards its expedient construction. In particular, the use of transition metal catalysis has demonstrated utility in constructing the requisite carbon-nitrogen bonds for formation of cyclic sulfamides. Highlighted in this chapter are efforts from several groups which achieve the synthesis of cyclic sulfamides by functionalization of an olefin using transition metal catalysis (other important transition metal-catalyzed methods for the synthesis of cyclic sulfamides are also discussed where deemed relevant). Mechanism is discussed where appropriate in order to frame the asymmetric synthesis of cyclic sulfamides by Pd-catalyzed carboamination reaction described in Chapter 4.

3.2 Developments in Transition Metal Catalyzed Synthesis of Cyclic Sulfamides

Chemler and coworkers demonstrated a highly diastereoselective synthesis of a variety of cyclic sulfamides using copper catalysis.[5] The reaction proceeds using stoichiometric amounts of copper(II) neodecanoate $[Cu(ND)]_2$ and potassium carbonate as base, and it achieves diastereomeric ratios up to >20:1 dr. The reaction achieves high diastereoselectivity by syn aminocupration as shown in **Scheme 3.1**. Investigation of a substrate with a deuterium-substituted olefin generated a product in which the diastereomeric ratio was 1:1. The scrambling of the stereocenter likely arises upon homolytic cleavage of the copper generating a primary radical which combines with another equivalent of $Cu(ND)_2$ in order to generate a Cu(III) species. This species facilitates the formation of the second C-N bond generating the bicyclic sulfamide.

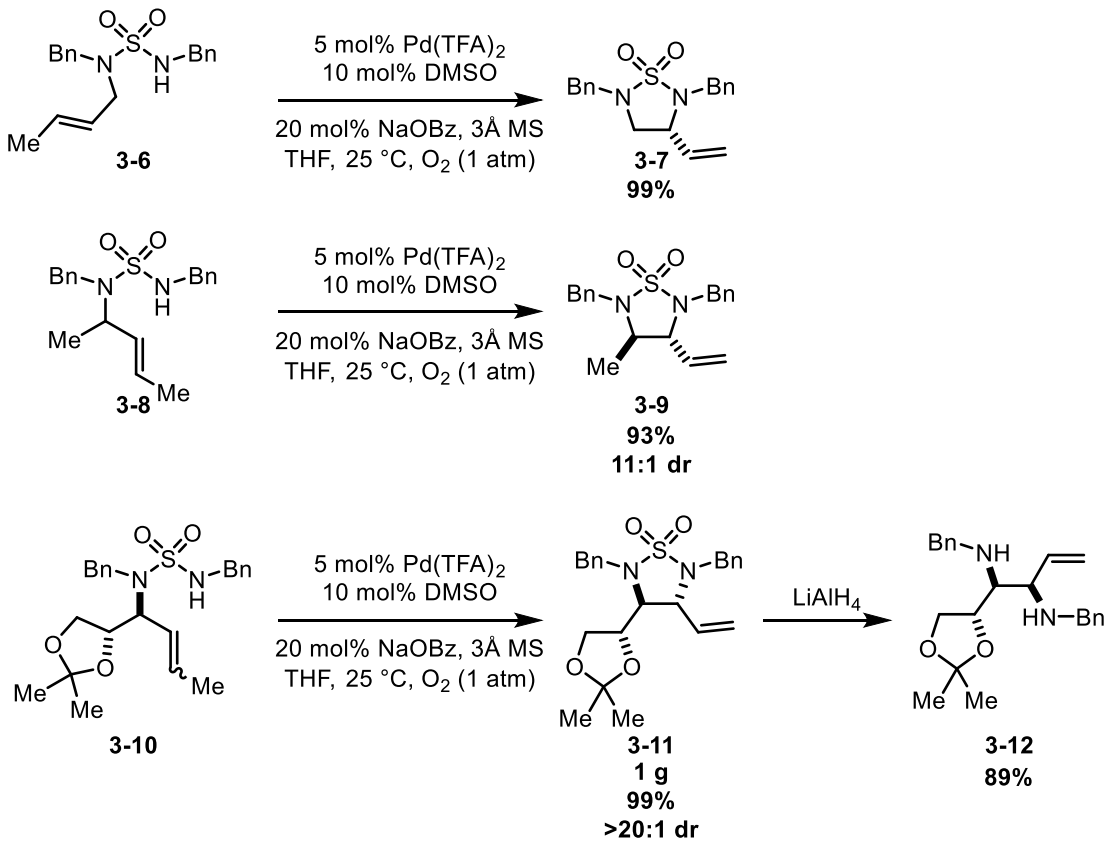
Scheme 3.1 Copper-Mediated Synthesis of Cyclic Sulfamides



The generation of cyclic sulfamides by a palladium-catalyzed oxidative protocol was demonstrated by Stahl and coworkers (**Scheme 3.2**).[6] This process utilizes catalytic amounts of $Pd(TFA)_2$ in the presence of oxygen, catalytic DMSO, and catalytic NaOBz to generate cyclic sulfamides in excellent yields (73% to 99%). The reaction proceeds in moderate (11:1 dr) to excellent (>30:1 dr) diastereoselecivity as the steric bulk of the allylic substituent increases.

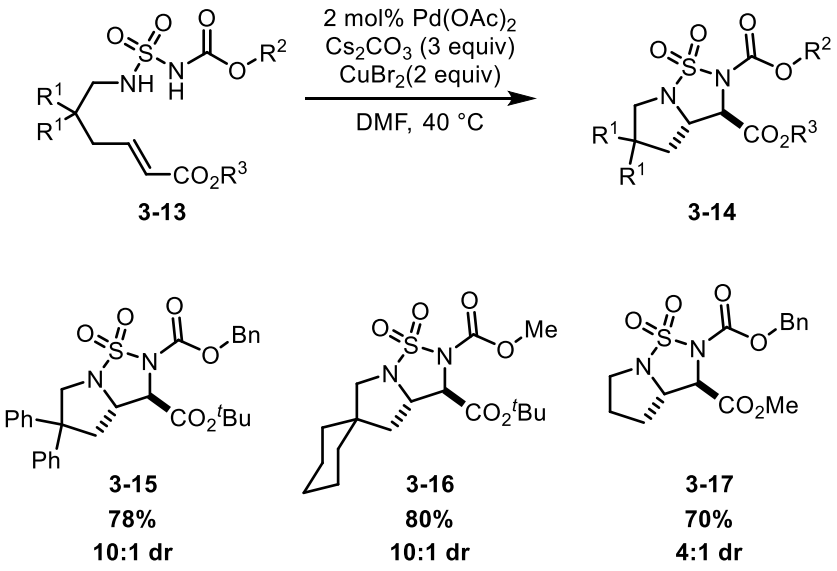
Two possible reaction mechanisms are proposed for this oxidative cyclization. The first mechanism proceeds by aminopalladation followed by β-hydride elimination, and the second mechanism proceeds by allylic C-H activation followed by C-N coupling. The authors suggests that the failure of a substrate bearing a homoallyl chain to undergo the cyclization indicates that the allylic C-H activation mechanism is not operative. In addition, the reaction can be conducted on gram scale, and the cyclic sulfamide **3-11** can be further elaborated to the chiral diamine **3-12** by reduction in the presence of $LiAlH_4$ in 89% yield.

Scheme 3.2 Palladium-Catalyzed Aerobic Oxidative Synthesis of Cyclic Sulfamides



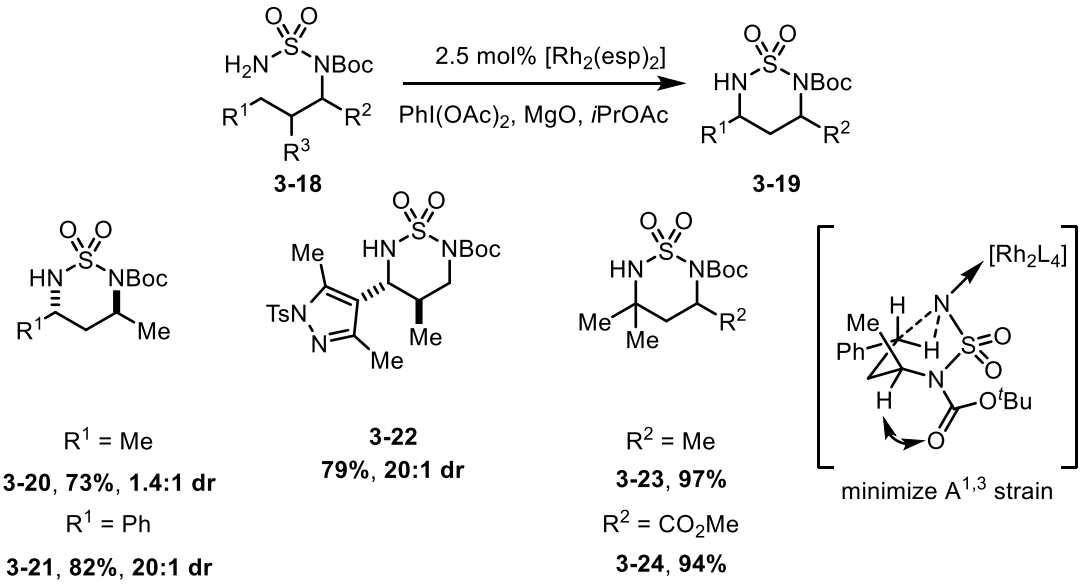
Bicyclic sulfamides were generated using an intramolecular diamination of acrylates as reported by Muñiz and coworkers.[7] The acrylate substrates were synthesized by a cross metathesis procedure beginning from the fully substituted sulfamide bearing a terminal olefin. The reaction proceeds using catalytic amounts of $Pd(OAc)_2$ along with 2 equiv of $CuBr_2$ as stoichiometric oxidant. The reaction proceeds with 10:1 dr as shown for **3-15** and **3-16**. The catalytic cycle presumably proceeds through a Pd(IV) species mediated by Cu which facilitates the second cyclization. The *trans* diastereomer which dominates in the products supports this catalytic cycle.

Scheme 3.3 Pd-Catalyzed Intramolecular Diamination of Acrylates to Form Bicyclic Sulfamides

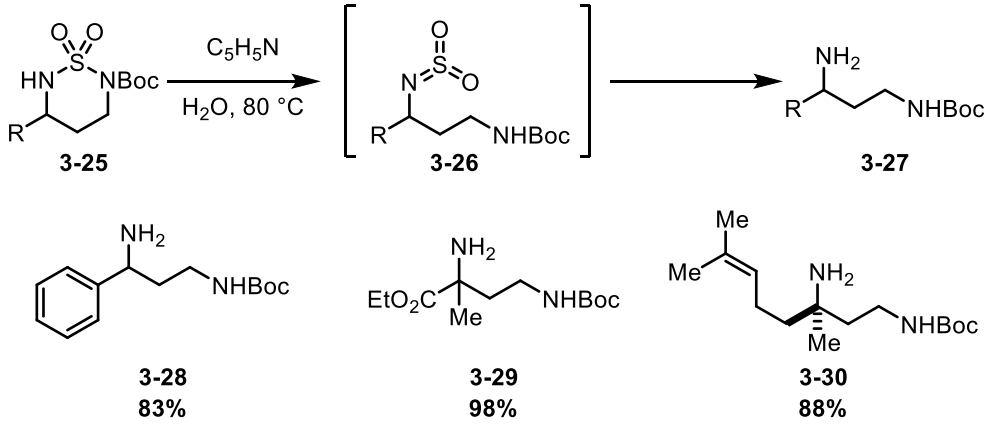


The Du Bois group achieved the synthesis of 1,3-diamines utilizing an intramolecular Rh-catalyzed C-H insertion strategy.[8] This reaction proceeds using 2.5 mol% $Rh_2(esp)_2$ and 1.1 equiv $PhI(OAc)_2$ as oxidant in the presence of MgO and ^{i}PrOAc. The reaction constructs 6-membered cyclic sulfamides which contain a variety of substitution patterns in good yields. In addition, high diastereoselectivity can be obtained for certain products like **3-21** and **3-22**. Different functional groups like esters as shown for the generation of **3-24** are additionally compatible with this reaction. The high diastereoselectivity is achieved by a transition state which minimizes $A^{1,3}$-strain between the boc protecting group on the sulfamide and substitution α to the substituted nitrogen. Finally, 1,3-diamines are readily accessed by heating the cyclic sulfamides with water and pyridine at 80 °C as shown in **Scheme 3.5**.

Scheme 3.4 Rh-Catalyzed C-H Insertion for Generating 6-Membered Cyclic Sulfamides



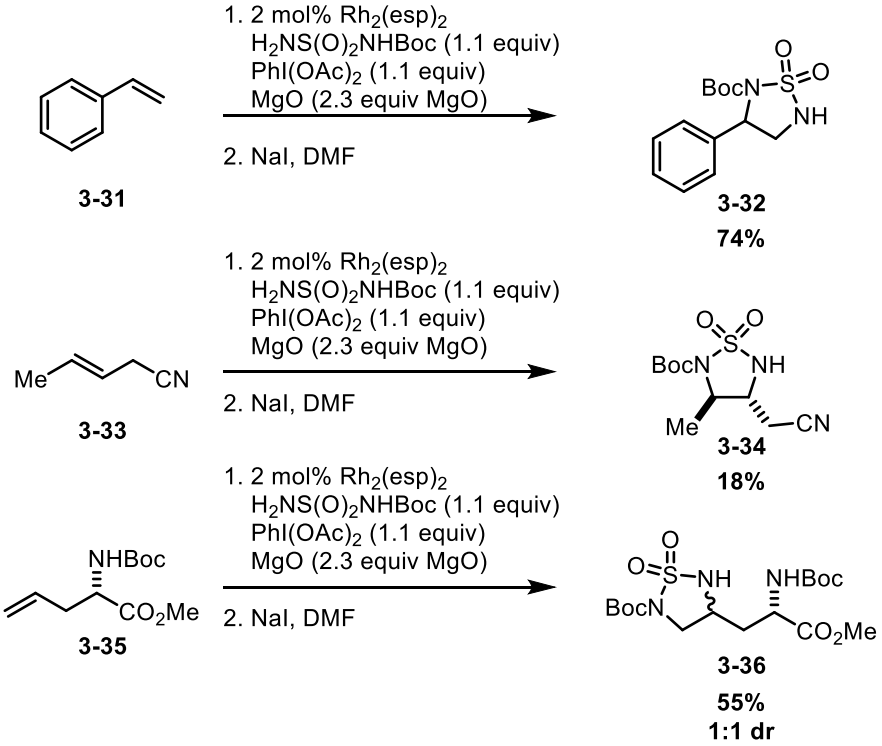
Scheme 3.5 Facile Ring-Opening to Afford 1,3-Diamines



More recent developments from the Du Bois group exhibit a method for the synthesis of cyclic sulfamides by a tandem Rh-catalyzed aziridination/NaI-promoted rearrangement sequence.[9] The development of this method sought an efficient means

for aziridination, and initial investigations unveiled *N*-carbamoyl sulfamides as competent substrates for the aziridination when 2 mol% of $Rh_2(esp)_2$ was used. It was hypothesized that a one-flask protocol for synthesizing cyclic sulfamides could be achieved by the addition of NaI and DMF once the aziridination reaction was complete. This tandem sequence works well for a variety of substrates as shown in **Scheme 3.6**. Reactions proceed in good yields and at times high diastereoselectivity (**3-34** was formed as a single stereoisomer).

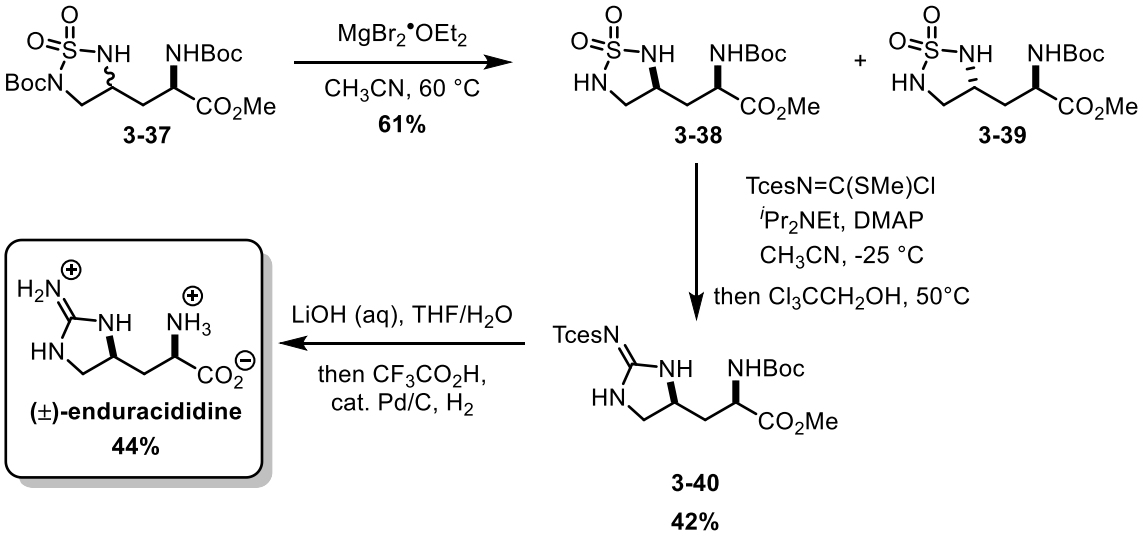
Scheme 3.6 Tandem Rh-catalyzed Aziridination-NaI Promoted Rearrangement for the Synthesis of Cyclic Sulfamides



The utility of this reaction is demonstrated in two ways. First, the cyclic sulfamides can be readily transformed to chiral 1,2-diamines in the same manner as

described above by reaction with pyridine/water at 80 °C (**Scheme 3.5**). Additionally, the total synthesis of (±)-enduracididine was achieved in only three steps (1. Chiral resolution; 2. Desulfonylation/guanylation; 3. Deprotection) from **3-37** as shown in **Scheme 3.7**. This natural product is an amino component of the macrocyclic polypeptide antibiotic enduracidin.

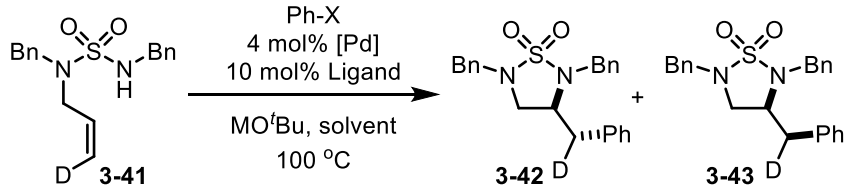
Scheme 3.7 Short Total Synthesis of (±)-Enduracididine



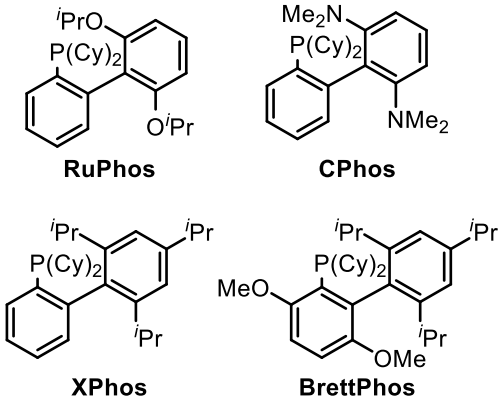
Wolfe and coworkers recently demonstrated a diastereodivergent strategy for accessing 5-membered cyclic sulfamides (**Table 3.1)**.[10] This reaction expands the scope of the Pd-catalyzed carboamination reaction which has been widely investigated by the Wolfe group.[11] Interestingly, the increased acidity of sulfamides permits control of diastereoselectivity by diverting mechanistic pathways based on careful selection of electrophile, ligand, base, and solvent.[12] In general, the *anti*-aminopalladation pathway

is favored by the use of aryl triflates, electron-rich Buchwald ligands, lithium *tert*-butoxide, and polar solvents like $PhCF_3$. Conversely, *syn*-aminopalladation pathways are favored by the use of aryl halides, XPhos as ligand, sodium *tert*-butoxide, and non-polar solvents like dioxanes or toluene. For example, deuterated substrate **3-41** is transformed with high diastereoselectivity (>20:1) to **3-42** by use of RuPhos or CPhos as ligand and $PhCF_3$ as solvent (**Table 3.8**, entry 1 and 12). In contrast, the use of XPhos in dioxane solvent or toluene solvent generate **3-43** with decent diastereoselectivity (**Table 3.8**, 1:10 dr for entry 4, 1:4 dr for entry 6). All in all, **Table 3.8** demonstrates that subtle changes to reaction conditions can drastically influence stereoselectivity in this Pd-catalyzed reaction.

Table 3.1 Diastereodivergent Synthesis of Cyclic Sulfamides



Entry	X	Ligand	M	Solvent	3-42:3-43
1	**OTf**	**RuPhos**	**Li**	**$PhCF_3$**	**>20:1**
2	OTf	RuPhos	Na	toluene	7:1
3	OTf	XPhos	Na	toluene	1:7
4	**OTf**	**XPhos**	**Li**	**dioxane**	**1:10**
5	OTf	XPhos	Li	$PhCF_3$	10:1
6	**Br**	**XPhos**	**Na**	**toluene**	**1:4**
7	Br	RuPhos	Na	toluene	1:1
8	Br	RuPhos	Na	toluene	1:1
9	Br	RuPhos	Na	$PhCF_3$	10:1
10	Br	XPhos	Na	$PhCF_3$	1:1
11	Br	BrettPhos	Na	$PhCF_3$	10:1
12	**Br**	**CPhos**	**Na**	**$PhCF_3$**	**>20:1**

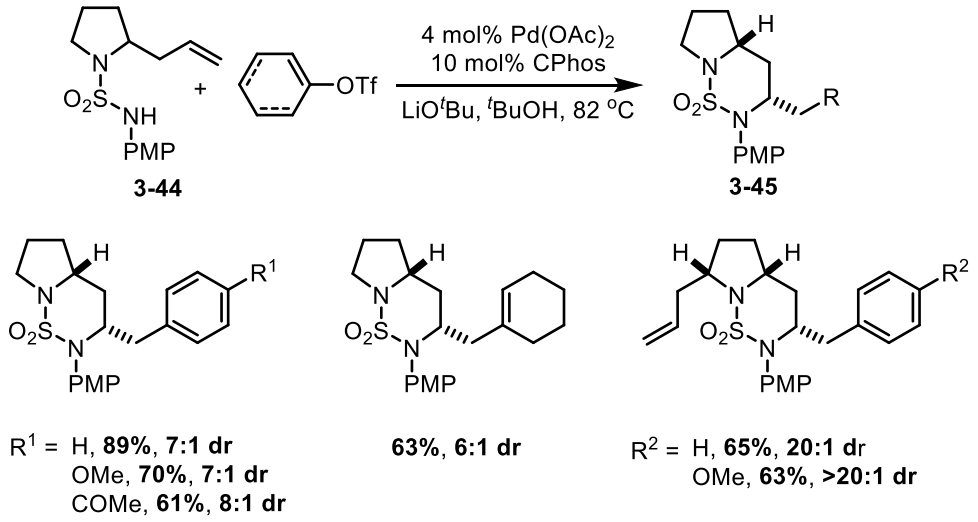


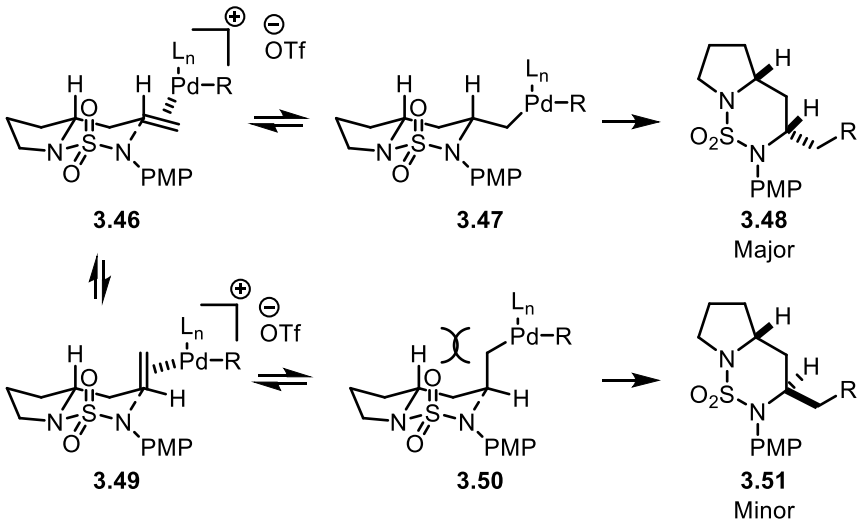
This diastereo-divergent method was further applied in the synthesis of bicyclic sulfamides by Wolfe and coworkers (**Scheme 3.8**).[13] Earlier work in the Wolfe group demonstrated that 1,3-bicyclic ureas were important retrons for the synthesis of batzelladine alkaloids.[14] Unfortunately, the carboamination reaction of ureas towards the stereoselective syntheses of this family of natural products is limited because these reactions proceed by a *syn*-aminopalladation mechanism; only merobatzelladine A and B contain the appropriate configuration that this mechanistic pathway can access.

Therefore, Wolfe and coworkers considered the viability of utilizing sulfamides as nucleophiles which can undergo *anti*-aminopalladation pathways thereby accessing the configuration more widely present in the batzelladine alkaloids (**Scheme 3.8**). To this end, the generation of bicyclic sulfamides was achieved using catalytic $Pd(OAc)_2$ and CPhos as ligand. Fewer side products derived from β-hydride elimination were generated when ^{t}BuOH was employed as the solvent. The reaction proceeds for a variety of aryl and alkenyl triflates with diastereoselectivity up to >20:1 dr.

The mechanistic pathway is shown in **Scheme 3.8**. Since the *anti*-aminopalladation pathway proceeds by pre-coordination of the olefin to the Pd catalyst, the attacking nitrogen of the sulfamide must attack from the backside. Two possible transitions states can occur under this system, and ultimately the major product **3-48** derives from a transition state which avoids steric interactions between the olefin and the hydrogen on the pyrrolidine ring.

Scheme 3.8 Synthesis of Bicyclic Sulfamides by Pd-Catalyzed Carboamination Reaction Bicyclic Sulfamides



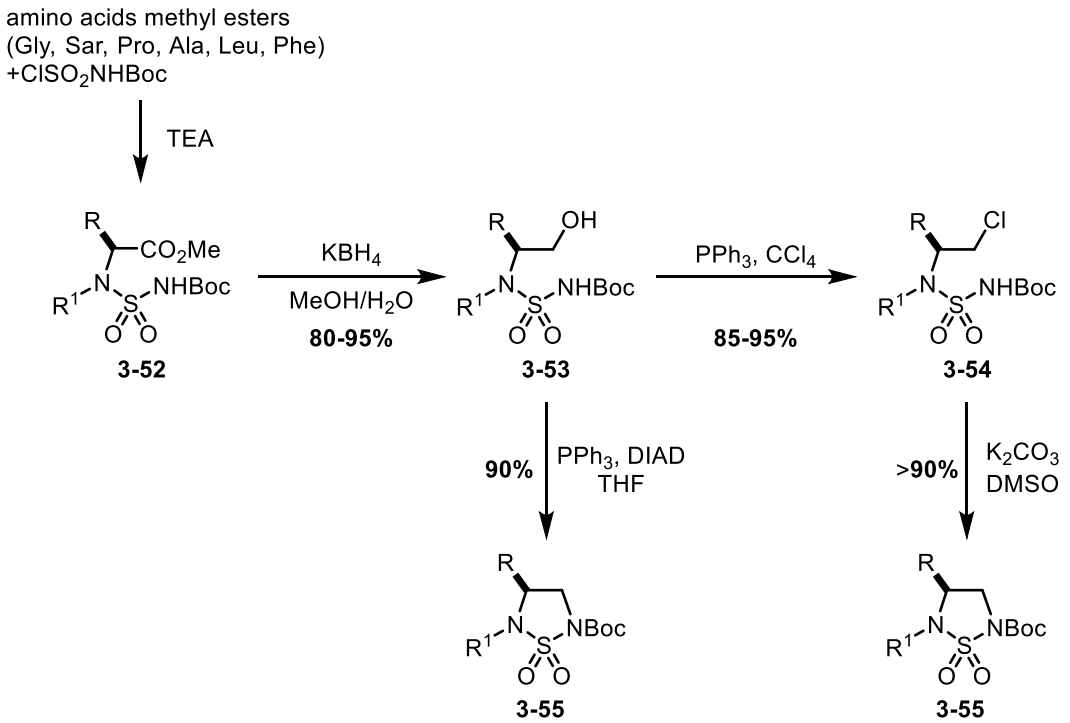


3.3 Developments in Asymmetric Synthesis of Cyclic Sulfamides

Despite the extensive amount of effort directed at the synthesis of cyclic sulfamides, little work has targeted efficient methods for producing cyclic sulfamides asymmetrically. In most instances, enantiomerically enriched cyclic sulfamides are

prepared by multistep routes from the corresponding amino acids. For example, **Scheme 3.9** shows the synthesis of cyclic sulfamides beginning with amino acid methyl esters.[15] The synthetic sequence proceeds by sulfonylation with $ClSO_2NHBoc$ which is followed by reduction of the methyl ester to the alcohol **3-53**. From here, a one-step Mitsunobu ring closure can provide cyclic sulfamide **3-55** or a two-step sequence consisting of Appel reaction/nucleophilic addition under basic conditions can also provide **3-55**.

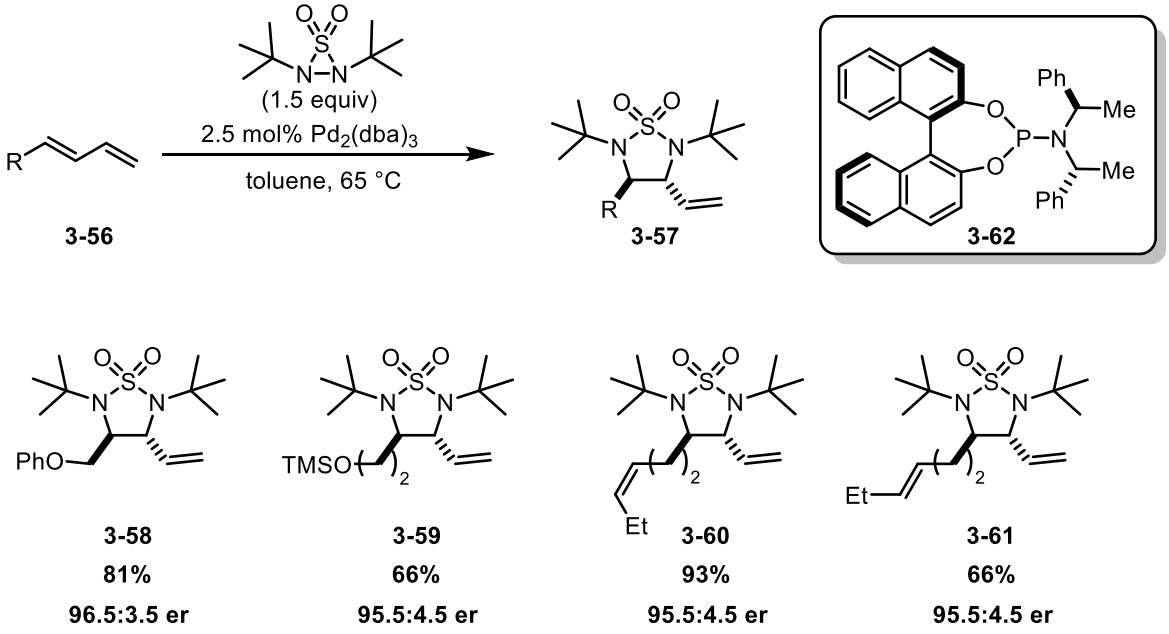
Scheme 3.9 Synthesis of Cyclic Sulfamides from Amino Acid Chiral Pool



Even though amino acids provide cyclic sulfamides in high enantiopurity, relying on this chiral pool restricts the chemical space which can be accessed. Therefore, new

methods which develop asymmetric catalysts, especially by implementation of transition metals, for generating cyclic sulfamides are highly desirable.

Scheme 3.10 Asymmetric Synthesis of Cyclic Sulfamides from Conjugated Dienes

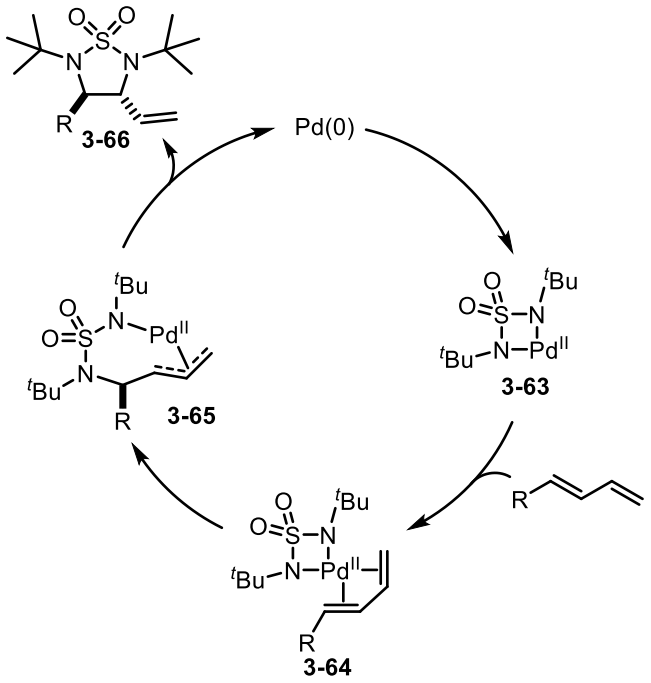


Only one group has provided enantioselective access to cyclic sulfamides using a transition metal catalyst. The Shi group has shown that cyclic sulfamides can be formed asymmetrically by reacting conjugated dienes with *N*,*N*'-di-*tert*-butylthiadiaziridine 1,1-dioxide in the presence of Pd(0) and a chiral phosphoramidite ligand.[16] Initial screening demonstrated that chiral phosphoramidite ligands were competent for inducing asymmetry and although several backbones were examined, the ligand that provided the best results derived from BINOL as shown in **Scheme 3.10**. These reactions afford a variety of cyclic sulfamides in high yields (up to 98%) and high

enantiopurity (96.5:93.5 er). Importantly, the reaction can selectively form the cyclic sulfamide in the presence of alkenes and protected alcohols.

The catalytic cycle proceeds by insertion of the chiral Pd(0) complex into the N-N bond of *N*,*N*'-di-*tert*-butylthiadiaziridine 1,1-dioxide (**Figure 3.2**). The Pd(II) complex **3-63** coordinates to the diene and undergoes migratory insertion to generate the π-allyl Pd complex **3-65**. Reductive elimination supplies the product and regenerates the chiral Pd(0) catalyst.

Figure 3.2 Catalytic Cycle for Asymmetric Synthesis of Cyclic Sulfamides from Conjugated Dienes



Although this reaction showcases a pragmatic disconnection for accessing enantioenriched cyclic sulfamides, it suffers from some limitations. First, *N*,*N*'-di-*tert*-

butylthiadiaziridine 1,1-dioxide is not commercially available. Second, the reaction requires acyclic conjugated dienes as coupling partners. These limitations highlight the need for efforts towards the developments of new chiral catalysts with broader scope. Chapter 4 will describe work toward developing a chiral catalyst for the generation of new cyclic sulfamides.

3.4 Conclusion

Cyclic sulfamides are widely present functional groups in natural products and pharmaceuticals rendering their expedient synthesis an important challenge for organic chemistry. Several groups have utilized transition metal catalysis for the synthesis of cyclic sulfamides, and many of these methods exploit olefins as a functional group handle for forging the required C-N bonds of the cyclic sulfamides. Despite the abundance of methods devised for generating cyclic sulfamides, little work has unveiled chiral catalysts for developing the asymmetric analogues of the racemic reactions. Only one example which utilized a Pd catalyst with a chiral phosphoramidite has achieved enantioselective synthesis of cyclic sulfamides. The shortage of asymmetric methods for this important functional group should therefore be addressed.

3.5 References

(1) (a) Reitz, A.B.; Smith, G.R.; Parker, M.H. *Expert Opin. Ther. Pat*. **2009**, *19*, 1449; (b) Spaltenstein, A.; Almond, M.R.; Bock, W.J.; Cleary, D.G.; Furfine, E.S.; Hazen, R.J.; Kazmierski, W.M.; Salituro, F.G.; Tung, R.G.; Wright, L.L. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1159; (c) Rosenberg, S.H.; Dellaria, J.F.; Kempf,

D.J.; Hutchins, C.W.; Woods, K.W.; Maki, R.G.; de Lara, E.; Spina, K.P.; Stein, H.H.; Cohen, J.; Baker, W.R.; Plattner, J.J.; Kleinert, H.D.; Perun, T.J.; *J. Med. Chem*. **1990**, *33*, 1582; (d) Dou, D.; Mandadapu, S.R.; Alliston, K.R.; Kim, Y.; Chang, K.O.; Groutas, W.C. *Eur. J. Med. Chem*. **2012**, *47*, 59; (e) Castro, J.L.; Baker, R.; Guiblin, A.R.; Hobbs, S.C.; Jenkins, M.R.; Russell, M.G.N.; Beer, M.S.; Stanton, J.A.; Scholey, K.; Hargreaves, R.J.; Graham, M.I.; Matassa, V.G. *J. Med. Chem*. **1994**, *37*, 3023; (f) Benltifa, M.; García Moreno, M.I.; Mellet, C.O.; García Fernández, J.M.; Wadouachi, A. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 2805; (g) Kim, S.J.; Jung, M.H.; Yoo, K.H.; Cho, J.H.; Oh, C.H. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 5815; (h) Dou, D.; Tiew, K.-C.; He, G.; Mandadapu, S.R.; Aravapalli, S.; Alliston, K.R.; Kim, Y.; Chang, K.O.; Groutas, W.C. *Bioorg. Med. Chem*. **2011**, *19*, 5975; (i) Brodney, M.A.; Barreiro, G.; Ogilvie, K.; Hajos-Korcsok, E.; Murray, J.; Vajdos, F.; Ambroise, C.; Christofferson, C.; Fisher, K.; Lanyon, L.; Liu, J.; Nolan, C.E.; Withka, J.M.; Borzilleri, K.A.; Efremov, I.; Oborski, C.E.; Varghese, A.; O'Neill, B.T. *J. Med. Chem*. **2012**, *55*, 9224.

(2) (a) Ahn, K.H.; Yoo, D.J.; Kim, J.S. *Tetrahedron Lett*. **1992**, *33*, 6661; (b) Fécourt, F.; Lopez, G.; Lee, A. V. D.; Martinez, J.; Dewynter, G. *Tetrahedron: Asymmetry*, **2010**, *21*, 2361.

(3) Pansare, S.V.; Rai, A.N.; Kate, S.N. *Synlett*, **1998**, 623.

(4) (a) Lucet, D.; Gall, T.L.; Mioskowski, C. *Angew. Chem. Int. Ed*. **1998**, *37*, 2580; *Angew. Chem*. **1998**, *110*, 2724; (b) Saibabu Kotti, S.R.S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des*. **2006**, *67*, 101; (c) Kizirian, J.C. *Chem. Rev*. **2008**, *108*, 140.

(5) Zabawa, T.P.; Chemler, S.R. *Org. Lett.* **2007**, *9*, 2035.

(6) McDonald, R.I.; Stahl, S.S. *Angew. Chem. Int. Ed.* **2010**, *49*, 5529.

(7) Chávez, P.; Kirsch, J.; Streuff, J.; Muñiz, K. *J. Org. Chem*. **2012**, *77*, 1922.

(8) Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2777.

(9) Olson, D.E.; Su, J.Y.; Roberts, D.A.; Du Bois, J. *J. Am. Chem. Soc.*, **2014**, *136*, 13506.

(10) Fornwald, R.M.; Fritz, J.A.; Wolfe, J.P. *Chem. Eur. J.* **2014**, *20*, 8782.

(11) For a review of Pd-catalyzed carboamination reactions, see Schultz, D.M.; Wolfe, J.P. *Synthesis*, **2012**, *44*, 351.

(12) For studies on factors that influence *syn*-versus *anti*-aminopalladation pathways in Wacker-type oxidative cyclizations of alkenes bearing pendant amines, see: a) Liu, G.; Stahl, S.S. *J. Am. Chem. Soc*. **2007**, *129*, 6328; b) Weinstein, A.B.; Stahl, S.S. *Angew.Chem. Int. Ed*. **2012**, 51, 11505; c) Ye, X.; White, P.B.; Stahl, S.S. *J. Org. Chem*. **2013**, *78* , 2083; d) Martínez, C.; Wu, Y.; Weinstein, A.B.; Stahl, S.S.; Liu, G.; Muñiz, K. *J. Org. Chem*. **2013**, *78*, 6309.

(13) Babij, N.R.; McKenna, G.M.; Fornwald, R.M.; Wolfe, J.P. *Org. Lett.* **2014**, *16*, 3412.

(14) (a) Babij, N. R.; Wolfe, J.P. *Angew. Chem*. **2012**, *124*, 4204; *Angew. Chem. Int. Ed*. **2012**, *51*, 4128; (b) Babij, N. R.; Wolfe, J.P. *Angew. Chem*. **2013**, *125*, 9417; *Angew. Chem. Int. Ed*. **2013**, *52*, 9247.

(15) Regaïnia, Z.; Abdaoui, M.; Aouf, N.-E.; Dewynter, G.; Montero, J.-L. *Tetrahedron*, **2000**, *56*, 381.

(16) Cornwall, R.G.; Zhao, B.; Shi, Y. *Org. Lett*. **2013**, *15*, 796.

Chapter 4

Asymmetric Synthesis of Cyclic Sulfamides

4.1 Background and Reaction Design

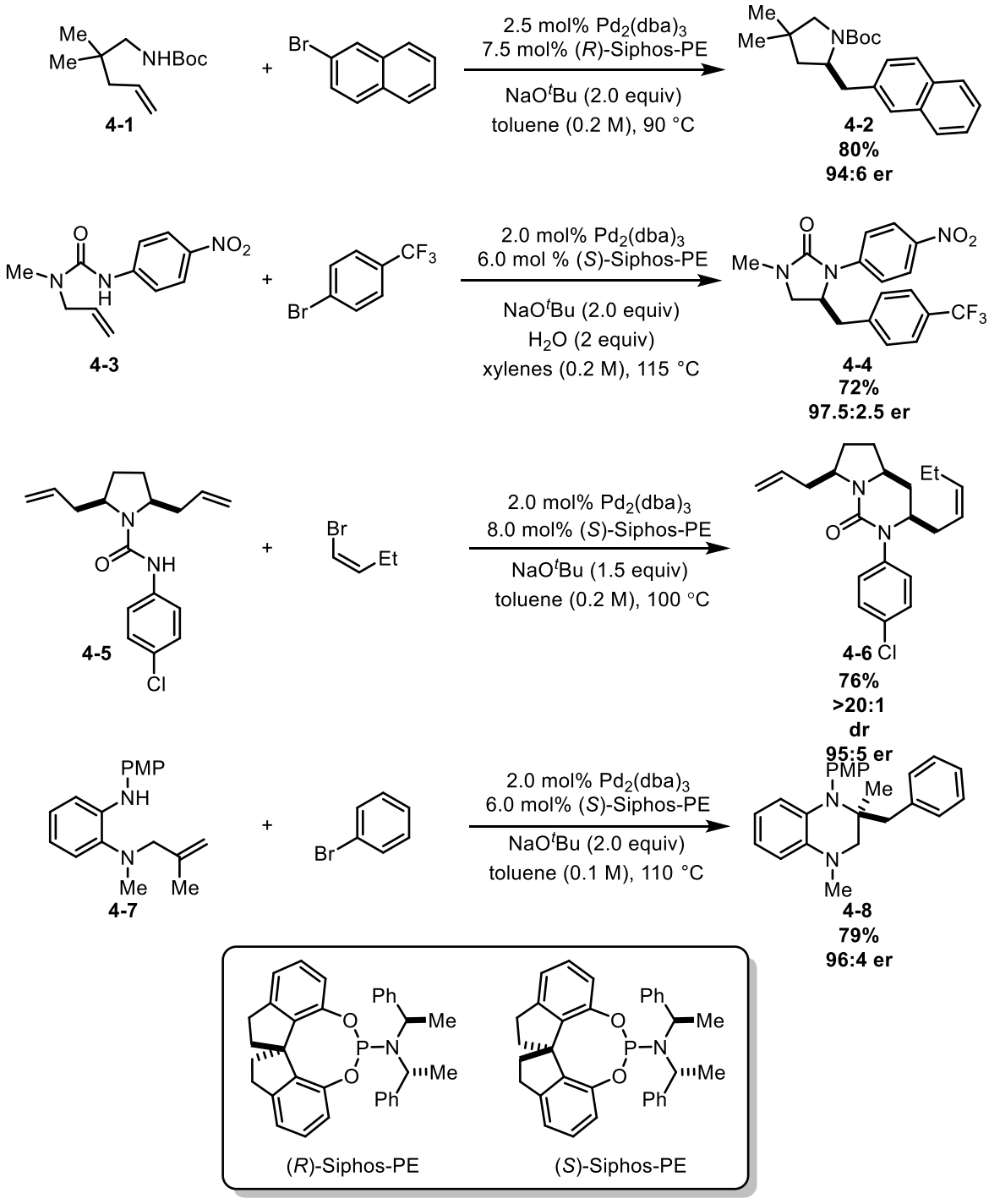
The development of a method for the asymmetric synthesis of cyclic sulfamides is rooted in the prior developments and knowledge gained from devising methods in the Wolfe group for the enantioselective synthesis of pyrrolidines,[1] ureas,[2] and benzofused heterocycles[3] as shown in **Scheme 4.1**. In all of the asymmetric reactions that have been developed monophosphorus ligands have been utilized.[4] Specifically, the chiral phosphoramidites (*R*)-Siphos-PE and (*S*)-Siphos-PE (which are actually diastereomers) have been the most effective ligands in asymmetric Pd-catalyzed carboamination reactions.

Besides the chiral environment induced by the ligand, the structure and electronics of the substrates affect the enantioselectivity. For example, the asymmetric synthesis of pyrrolidines relied on geminal substitution in the backbone of the boc-protected allylamine in order to achieve greater than 95:5 er. Also, consider the variety of different protecting groups on the cyclizing nitrogen in each of these reactions. Each protecting group is different, and this is due to each reaction operating slightly differently. In the case of the desymmetrization of *meso*-2,5-diallyl ureas, *p*-NO_2 substitution on the protecting group actually achieved higher levels of enantioselectivity

in similar fashion to the asymmetric synthesis of imidazolidin-2-ones, but the chemical yield was not satisfactory. The optimal protecting group which balanced good yield, dr, and er was *p*-Cl-phenyl. Informed by the important influence of substrate structure and electronics, corollary asymmetric reactions can be achieved.

With the insight garnered from these previous developments, an asymmetric synthesis of cyclic sulfamides seemed feasible. Cyclic sulfamides are isosteres of ureas so utilizing conditions that were successful for generating enantiopure imidazole-2-ones would be a good starting point. In addition, protecting groups on the sulfamide nitrogens could influence the enantioselectivity favorably. As this asymmetric reaction of sulfamides was considered, the competing *anti*/*syn* aminopalladation mechanistic dichotomy[5] was at the forefront of the reaction design. It was hoped that using conditions that were successful for the ureas, which operated under conditions that promote *syn* aminopalladation conditions, would also bias the mechanistic pathway so that this competition would not be ruinous to the development of enantiopure compounds. Also, finding a chiral ligand which enables successful carboamination reaction under *anti* aminopalladation conditions could provide a enantioselective diastereodivergent method for the synthesis of cyclic sulfamides. Efforts towards method development under both mechanistic frameworks is described below.

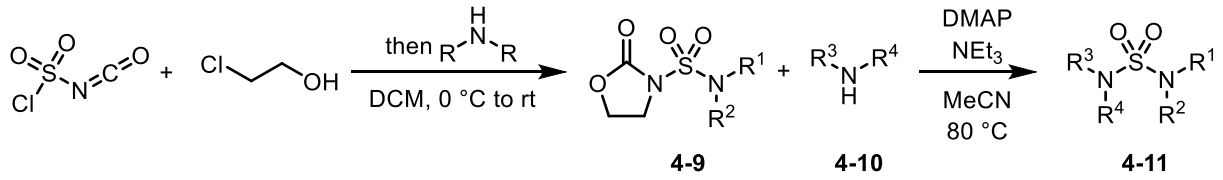
Scheme 4.1 Prior Developments in Asymmetric Carboamination Reactions



4.2 Substrate Synthesis

The sulfamide substrates are readily formed in one step by a sulfonylation protocol (**Scheme 4.2**).[6] The desired secondary amine is reacted with a desired oxazolidine in order to produce the material. The desired oxazolidines can be made in one step for a variety of different amines.

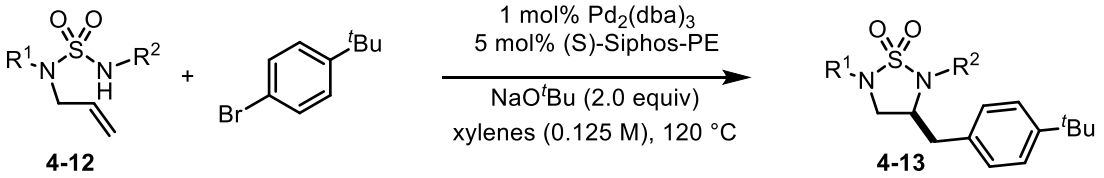
Scheme 4.2 Substrate Synthesis



4.3 Reaction Optimization for Synthesis of 5-Membered Cyclic Sulfamides

Investigations into the asymmetric synthesis of 5-membered cyclic sulfamides were initiated by exploring the role of different protecting groups on the sulfamide. Protecting groups that could be readily cleaved were targeted. In addition, the catalyst that was successfully employed for the synthesis of cyclic ureas was also used during this study. As shown in **Table 4.1**, entry 1-4, substrates bearing several different protecting groups failed to undergo successful cyclization. However, when a *tert*-butyl substituent was utilized as the protecting group, 70% of the desired product was formed with great enantioselectivity (93:7 er). At this point, other cleavable protecting groups on the cyclizing nitrogen were examined, but no other group improved the enantioselectivity beyond that attained in entry 5. Therefore, the electrophile scope was examined with a sulfamide bearing a *tert*-butyl group on the non-cyclizing nitrogen and a benzyl group on the cyclizing nitrogen.

Table 4.1 Optimization by Protecting Group Investigation



Entry	R^1	R^2	Yield	Enantiomeric Ratio
1	Bn	Bn	0%	N/A
2	*p*OMe-Ph	Bn	0%	N/A
3	*p*Cl-Ph	Bn	0%	N/A
4	benzhydryl	Bn	0%	N/A
5	**^{t}Bu**	**Bn**	**70%**	**93:7**
6	^{t}Bu	*p*OMe-Ph	47%	78:22
7	^{t}Bu	*p*Cl-Ph	11%	73:27
8	^{t}Bu	*p*OMe-Bn	79%	85:15
9	^{t}Bu	*p*NO_2-Bn	0%	N/A
10	^{t}Bu	*m*OMe-Bn	60%	91:9

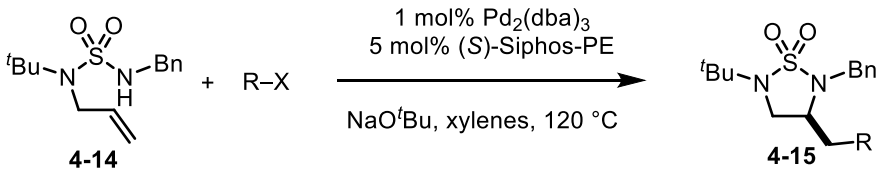
4.4 Reaction Scope for Asymmetric Synthesis of 5-Membered Cyclic Sulfamides

The reaction is effective for a variety of electrophiles. In general, electrophiles bearing electron-rich substituents like those shown for **4-15,** entry 5 and **4-15**, entry 6 achieved higher levels of enantioselectivity whereas electrophiles bearing electron-deficient groups like those shown for **4-15**, entry 9 and **4-15**, entry 10 are transformed with lower selectivity. The use of alkenyl electrophiles produced cyclic sulfamides in high enantioselectivity (up to 95:5 er), but these reactions suffered from low chemical yield due to competing Heck arylation reactions. Steric bulk on the electrophile is not

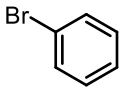
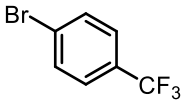
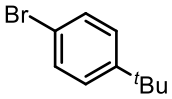
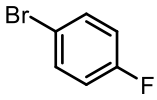
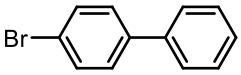
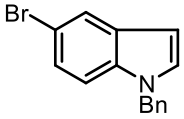
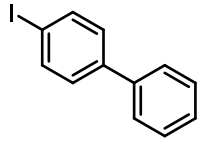
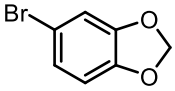
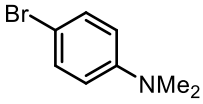
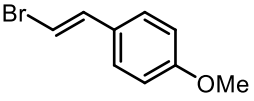
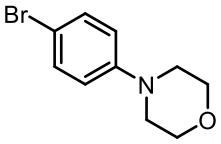
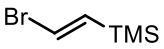
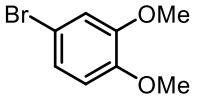
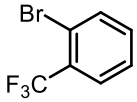
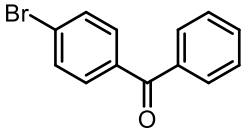
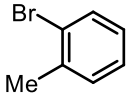
tolerated well as demonstrated for entry 15 and entry 16 where the highest levels of enantioselectivity were 74:26. Finally, transformations which utilized electrophiles derived from heterocycles (see **Table 4.2,** entry 11 and 12) proceeded in 92:8 er.

The addition of water exhibited a remarkable influence on the asymmetric reaction. In the asymmetric Pd-catalyzed carboamination reaction for the synthesis of imidazolidin-2-ones, the addition of 2 equiv of water improved the enantioselectivity for electron poor electrophiles. Interestingly, the addition of 2 equiv of water to the Pd-catalyzed reaction for the synthesis of cyclic sulfamides does not have a remarkable influence on enantioselectivity; instead, the yields were improved by the addition of water by up to 45%. While the role of water is not entirely clear, it may play a role in suppressing competing decomposition of the substrate which occurs over the course of long reaction times.

Table 4.2 Electrophile Scope for Generating 5-Membered Cyclic Sulfamides[a]



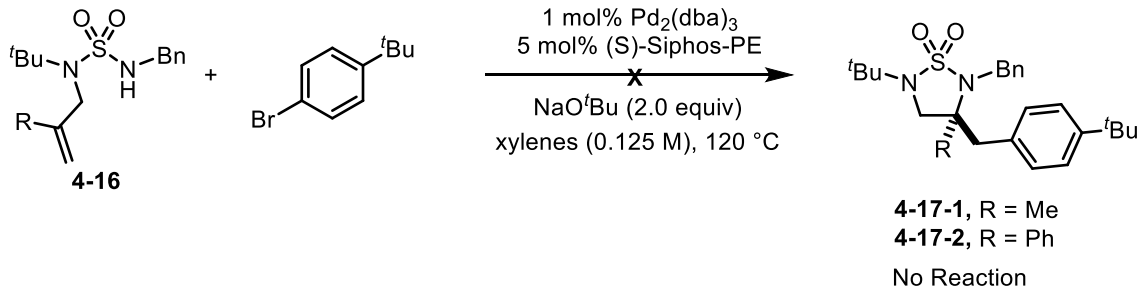
4-14 **4-15**

Entry	R	Yield[b]	er[c]	Entry[a]	R	Yield[b]	er[c]
1		51% **96%**	93:7 **93:7**	9		62% **67%**	89:11 **93:7**
2		65% **88%**	94:6 **94:6**	10		53% **69%**	88:12 **90:10**
3		62% **95%**	94:6 **94:6**	11		60% **72%**	90:10 **92:8**
4		46% **77%**	81:19 **75:25**	12		50% **74%**	91:9 **92:8**
5		48% **85%**	94:6 **95:5**	13		56% **44%**	94:6 **94:6**
6		70% **89%**	94:6 **94:6**	14		44% **34%**	93:7 **95:5**
7		67% **75%**	94:6 **94:6**	15		22% **21%**	57:43 **62:38**
8		65% **74%**	87:13 **90:10**	16		46% **58%**	76:24 **68:32**

[a]Conditions: 1.0 equiv. substrate **4-14**, 2.0 equiv. of R-X, 2.0 equiv of NaO^{t}Bu, 1 mol% [$Pd_2(dba)_3$], 5 mol% *S*-SIPHOS-PE, xylenes (0.125 M), 120 °C, 18 h. Reactions were conducted on a 0.30 mmol scale. [b]Isolated yield (average of two or more runs). Bolded and underlined yields were obtained by conducting the reaction with 2 equiv of water. [c]Enantiomeric ratios were determined by chiral HPLC analysis. Bolded and underlined enatiomeric ratios were obtained by conducting the reaction with 2 equiv of water.

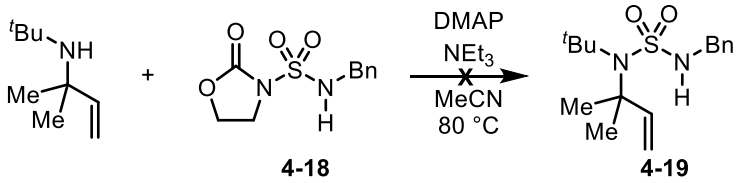
While this method is effective for a variety of electrophiles, other sulfamide substrates failed to achieve desirable reactivity. For example, different substitution patterns around the olefin failed to generate the cyclic sulfamides. First, 1,1-disubstituted alkenes, where R = Me or Ph as shown in **Scheme 4.3,** were unsuccessful under the optimized reaction conditions. The reactions afford starting material or the starting material undergoes decomposition.

Scheme 4.3 Limitations for Generating 5-Membered Cyclic Sulfamides



Additionally, attempts were made to synthesize sulfamide substrates bearing symmetric geminal substitution in the allylic position like **4-13** in **Scheme 4.4** in order to extend substrate scope. Unfortunately, the synthesis of these substrates was unsuccessful, presumably due to excess steric bulk around the amine inhibiting the required sulfonylation.

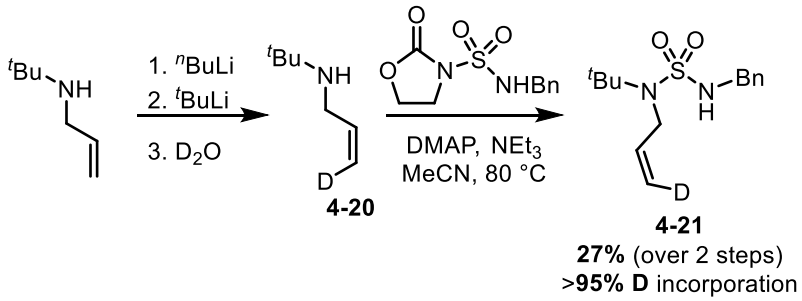
Scheme 4.4 Limitations for Generating 5-Membered Acyclic Sulfamides



4.5 Mechanistic Investigations: *Syn* or *Anti* Aminopalladation Mechanism?

Since *anti* aminopalladation and *syn* aminopalladation mechanistic pathways are competitive for the carboamination reaction of sulfamides, deuterated substrate **4-16** was synthesized in two steps to evaluate the primary mode of reactivity. First, commercially available *tert*-butyl allylamine was deuterated under basic conditions followed by the requisite sulfonylation reaction. The desired deuterated substrate was formed in 27% yield over 2 steps with >95% deuterium incorporation.

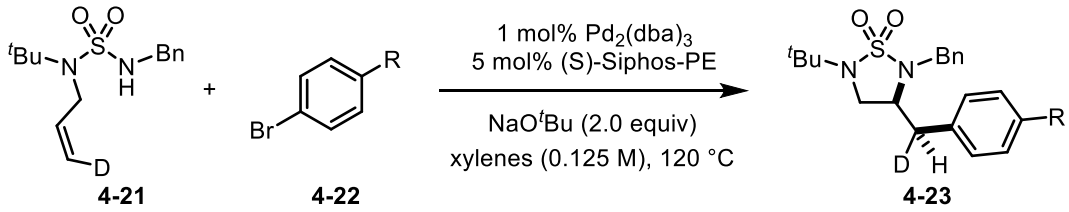
Scheme 4.5 Synthesis of Deuterated Substrate **4-21**



The carboamination reaction was conducted with a variety of electrophiles to examine if electronics influenced the diastereoselectivity. As shown in **Table 4.3**, all the electrophiles demonstrated that the *syn* aminopalladation pathway was the dominant

pathway. Interestingly, both the diastereoselectivity and enantioselectivity when 4-bromobenzotrifluoride was used as the electrophile (entry 4) was lower than when 4-^{t}Bu-C_6H_4Br was used as the electrophile (entry 1).

Table 4.3 Synthesis of Deuterated Products Derived from **4-21**[a]



4-21 **4-22** **4-23**

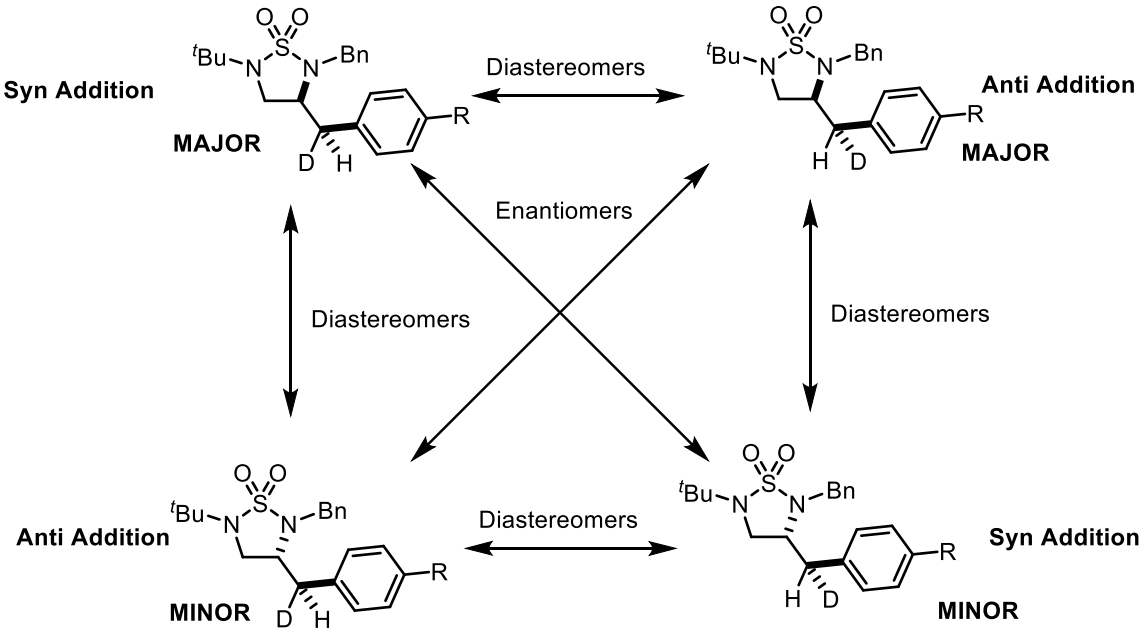
Entry	R	Yield (%)[b]	dr[c]	er[d]
1	^{t}Bu	58%	17:1	94:6
2	H	67%	8:1	95:5
3	Ph	65%	9:1	92:8
4	CF_3	58%	7:1	88:12
5[e]	CF_3	78%	5:1	89:11

[a]Conditions: **4-21** (1.0 equiv), Ar-Br (2.0 equiv), NaO^{t}Bu (2.0 equiv), [$Pd_2(dba)_3$] (1 mol%), (*S*)-Siphos-PE (5 mol%), xylenes (0.125 M), 120 °C, 18 h; reactions were conducted on a 0.25 mmol scale. [b]Isolated yield (result of a single experiment). [c] Diastereomeric ratios were determined by ^{1}HNMR integration. [d]Enantiomeric ratios were determined by chiral HPLC analysis. [e]The reaction was conducted with 2.0 equiv of water added.

This correlation between lower enantioselectivity and lower diastereoselectivity may indicate that the use of electron deficient electrophiles increases *anti*-aminopalladation pathways which lowers enantioselectivity. While this correlation is interesting, more mechanistic analysis is required to determine if *anti* aminopalladation pathways actually are interwoven with enantioselectivity.

It should be noted that the data outlined in **Table 4.3** does not take into account that 4 potential compounds can be formed in the reaction as shown in **Figure 4.1**. The data obtained consists of mixtures of 4 compounds. The diastereoselectivity was determined by H^1 NMR analysis of the mixture of the four compounds while the enantioselectivity was determined by chiral HPLC analysis of the four compounds.

Figure 4.1 Possible Formation of Four Compounds from Deuterated Substrate **4-21**



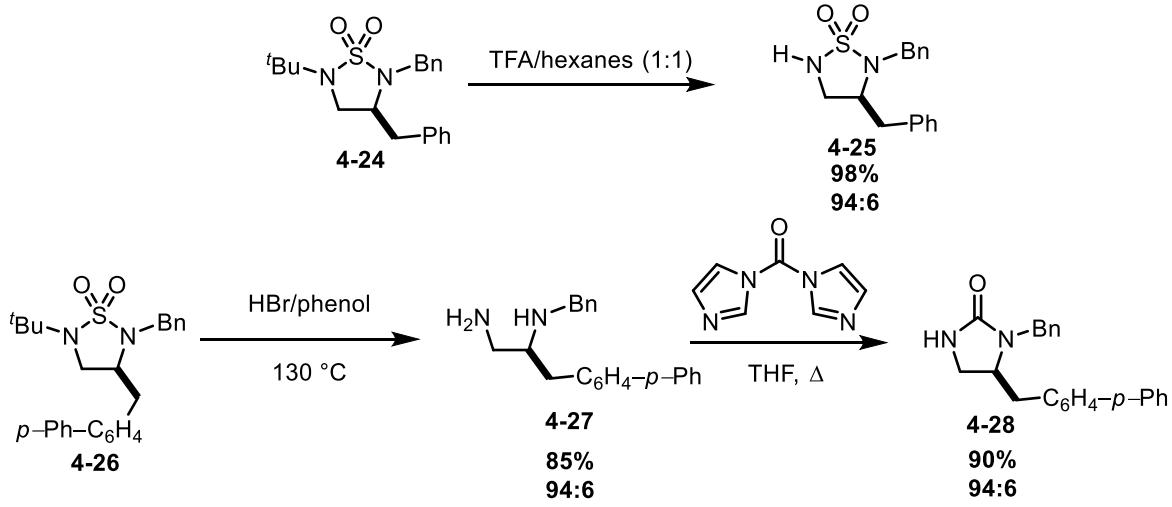
To properly determine the ratios of the four compounds, a third set of data is needed: an H^1 NMR analysis of one set of the HPLC peaks which could be isolated by preparative chiral HPLC analysis. This type of mechanistic analysis was performed by Weinstein and Stahl for studying the nucleopalladation pathways of Wacker-type

cyclizations.[7] In order to fully determine the relationship between *anti* and *syn* aminopalladation pathways and enantioselectivity, this third data set is a necessity. Without this piece of data, the only conclusion that can be made is that the dominant mechanistic pathway is *syn* aminopalladtion; any conjecture regarding the relationship between enantioselectivity and the mechanistic pathway is only speculative. This will be the subject of future studies by the Wolfe group for unraveling the influence of electronics of the aryl halide on the mechanistic outcome.

4.6 Methods for Deprotection

To demonstrate the synthetic utility of the method, deprotection strategies were evaluated as shown in **Scheme 4.6**. First, the *tert*-butyl protecting group could be selectively cleaved in the presence of trifluoroacetic acid which produced the free cyclic sulfamide **4-25** in 98% yield while maintaining the enantiopurity (94:6 er). Second, the sulfur dioxide component of the cyclic sulfamide in tandem with the *tert*-butyl protecting group could be removed by reaction with hydrobromic acid in the presence of phenol at elevated temperatures (130 °C). This provided chiral diamine **4-27** in good yield with enantiopurity intact. Chiral diamine **4-27** was further elaborated by reaction with 1,1′-carbonyldiimidazole so that the enantiopurity could be evaluated by chiral HPLC.

Scheme 4.6 Deprotecting 5-Membered Cyclic Sulfamides



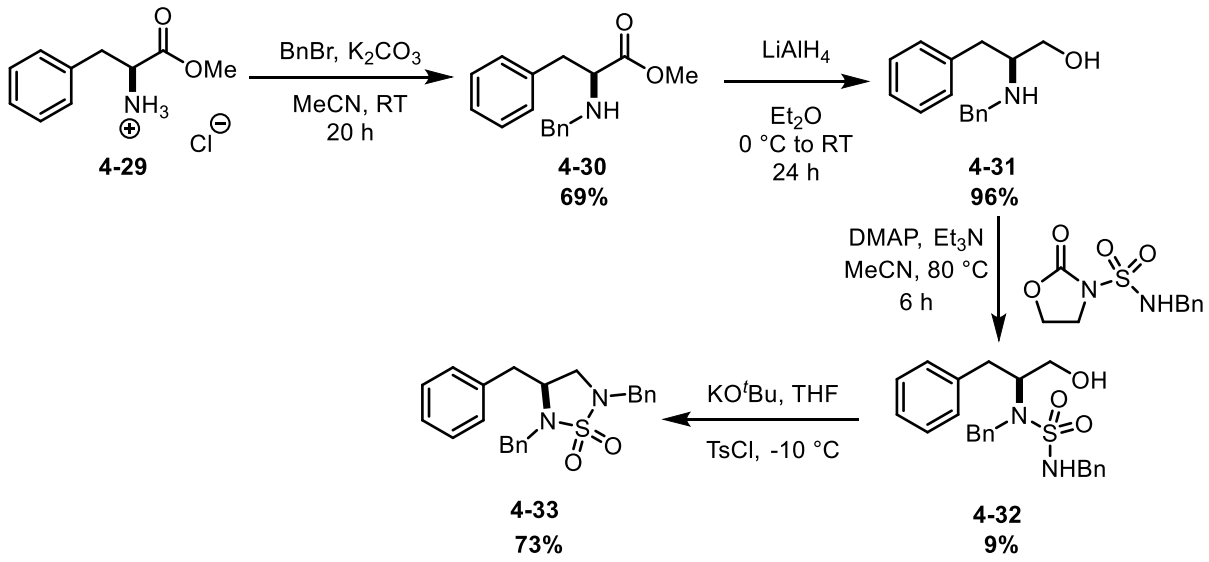
4.7 Synthesis of Authentic Sample for Determining Absolute Configuration

The synthesis of an authentic sample of **4-33** was accomplished beginning with L-phenylalanine methyl ester hydrochloride as shown in **Scheme 4.7**. First, the amine is alkylated with BnBr followed by reduction of the methyl ester to the alcohol (66% yield over two steps). Then, sulfonylation with the requisite oxazolidinone proceeded to give the desired intermediate **4-32** albeit in low yield (9%). The low yield likely derives from competing sulfonylation of the alcohol which produces undesired side products. Then, a one pot tosylation/alkylation sequence formed the desired authentic sample **4-33**.

The synthesis of this authentic sample highlights the advantage of utilizing the Pd-catalyzed method described for the synthesis of chiral cyclic sulfamides. Only two steps (starting from commercially available *N*-*tert*-butyl allylamine) are required to generate chiral cyclic sulfamides whereas the synthesis outlined in **Scheme 4.7** requires 4 steps from the already protected amino acid. Additionally, the method

described in this chapter expands the chemical space which the use of amino acids otherwise restricts for generating chiral cyclic sulfamides.

Scheme 4.7 Synthesis of an Authentic Sample

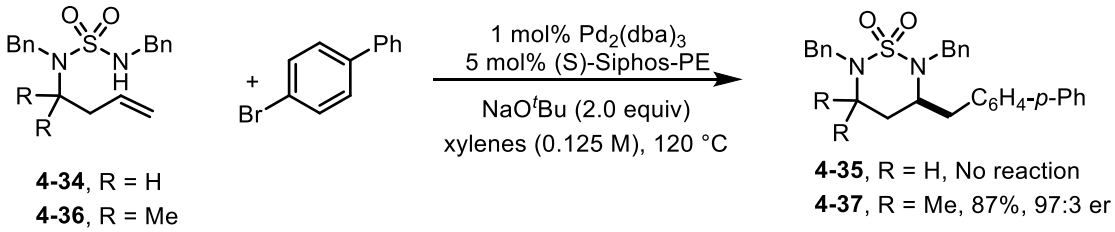


4.8 Asymmetric Synthesis of Monocyclic 6-Membered Cyclic Sulfamides

Currently, *no* methods are available to generate 6-membered cyclic sulfamides asymmetrically despite the abundance of methods available for generating the racemic counterparts. Therefore, the development of an asymmetric synthesis of 6-membered sulfamides could prove useful to the synthetic community, especially since these sulfamides could also serve as precursors to enantiopure 1,3-diamines. Also, the substrate scope for the synthesis of 5-membered cyclic sulfamides was limited in that only one sulfamide was competent for the reaction.

In an attempt to expand the substrate scope of the reaction described in **Scheme 4.8**, substrate **4-34** bearing a homoallyl chain was synthesized in order to test under the reaction conditions. This substrate failed to achieve desirable reactivity. Because the cyclization of 5-membered sulfamides relies heavily on the *tert*-butyl group for successful cyclization, substrate **4-36** was synthesized to test the plausibility of a Thorpe-Ingold-induced asymmetric cyclization to form monocyclic 6-membered cyclic sulfamides. The geminal substitution of substrate **4-36** enabled the successful cyclization to form **4-37**, the first enantiopure monocyclic 6-membered sulfamide generated via asymmetric catalysis. The yield (87%) and er (97:3) were remarkably high, so no further optimization of the reaction conditions took place.

Scheme 4.8 Cyclization of Sulfamides Bearing Homoallyl Chains



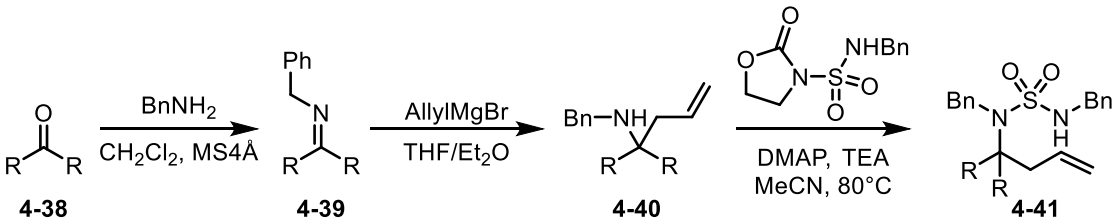
4-34, R = H
4-36, R = Me

4-35, R = H, No reaction
4-37, R = Me, 87%, 97:3 er

In most instances, the substrates for making 6-membered cyclic sulfamides were synthesized in the same fashion as for making 5-membered cyclic sulfamides (in this case, sulfonylation of the homoallylamine is required to form the substrate). While most allyl amines were made by alkylation of allylamine or allylbromide, the synthesis of homoallylamines was unique due to the requisite geminal substitution needed for cyclization.

The homoallylamines were made by the two-step protocol shown n **Scheme 4.9**. First, an imine is formed by reacting a ketone with an amine in the presence of molecular sieves and methylene chloride. Then, the imine is subjected to a Grignard reaction with allylmagnesium bromide (or other Grignard reagent). This forms the desired homoallyl amine which is then subjected to sulfonylation in the presence of *N*-benzyl-2-oxooxazolidine-3-sulfonamide to generate the desired sulfamide precursor.

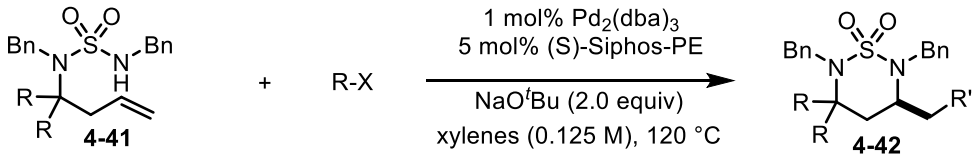
Scheme 4.9 Synthesis of Homoallyl amine Precursors for Synthesizing Sulfamide Substrates

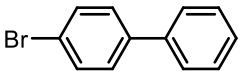
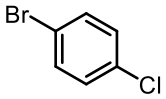
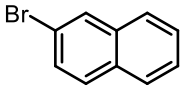
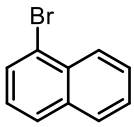
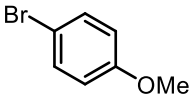
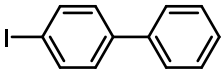
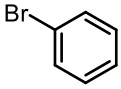
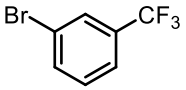
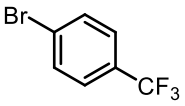
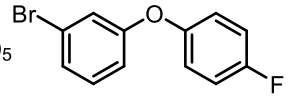
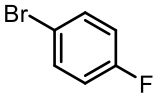
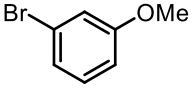


Thus far, the electrophile scope of the reaction is quite expansive. The use of electron-rich or electron poor electrophiles generates sulfamides with greater than 95:5 er. The use of ortho-substituted electrophiles causes the enantioselectivity to drop to 85:15 er, and the use of aryl iodides forms sulfamides with lower and irreproducible enantiomeric ratios. The essential geminal substitution can also be changed to either ethyl or cyclohexyl while maintaining great results (entry 9, 11-13). Future studies will be directed towards the use of alkenyl halides as electrophiles in this reaction.

Table 4.4 Substrate Scope for Synthesis of

Enantiopure 6-membered Cyclic Sulfamides[a]



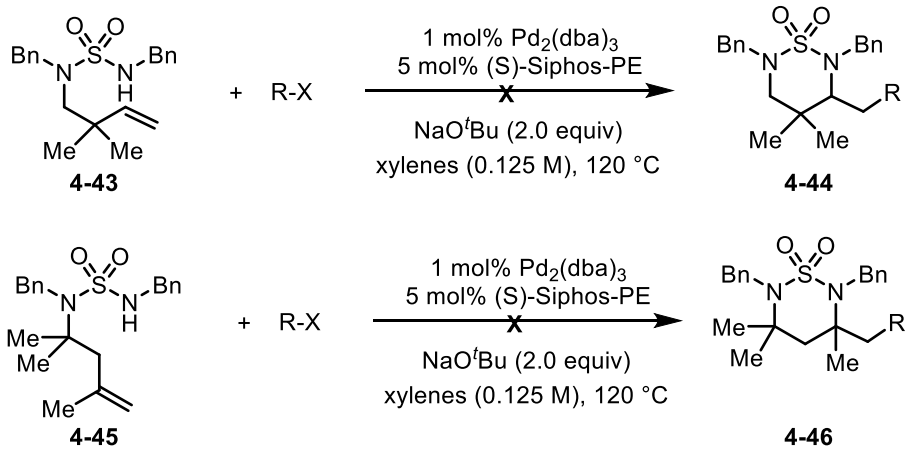
Entry	R	R'-X	Yield[b]	er[c]	Entry	R	R'-X	Yield[b]	er[c]
1	Me		87%	97:3	7	Me		65%	96:4
2	Me		75%	96.5:3.5	8	Et		92%	95:5
3	Me		57%	98:2	9	Me		42%	82:18-91.5:8.5
4	Me		93%	95:5	10	$(CH_2)_5$		92%	96.5:3.5
5	Me		75%	96.5:3.5	11	$(CH_2)_5$		92%	96:4
6	Me		94%	96.5:3.5	12	$(CH_2)_5$		90%	97:3

[a]Conditions: 1.0 equiv. substrate, 2.0 equiv. of R-X, 2.0 equiv of NaO^{t}Bu, 1 mol% [$Pd_2(dba)_3$], 5 mol% S-SIPHOS-PE, xylenes (0.125 M), 120 °C, 18 h. Reactions were conducted on a 0.20 mmol scale. [b]Isolated yield (average of two or more runs).[c]Enantiomeric ratios were determined by chiral HPLC analysis

Like the 5-membered cyclic sulfamides, the cyclization to form 6-membered cyclic sulfamides suffers from limitations. First, attempted cyclizations of substrate **4-43**

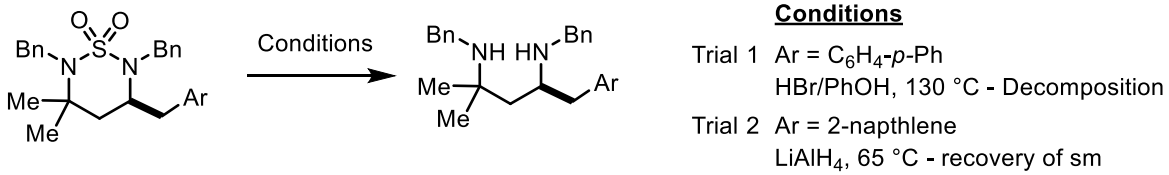
which contains geminal substitution in the allylic position did not undergo desired reactivity. Additionally, substrate **4-45** which contained a 1,1-disubstituted alkene failed.

Scheme 4.10 Substrate Scope Limitations for Synthesis of 6-Membered Cyclic Sulfamides



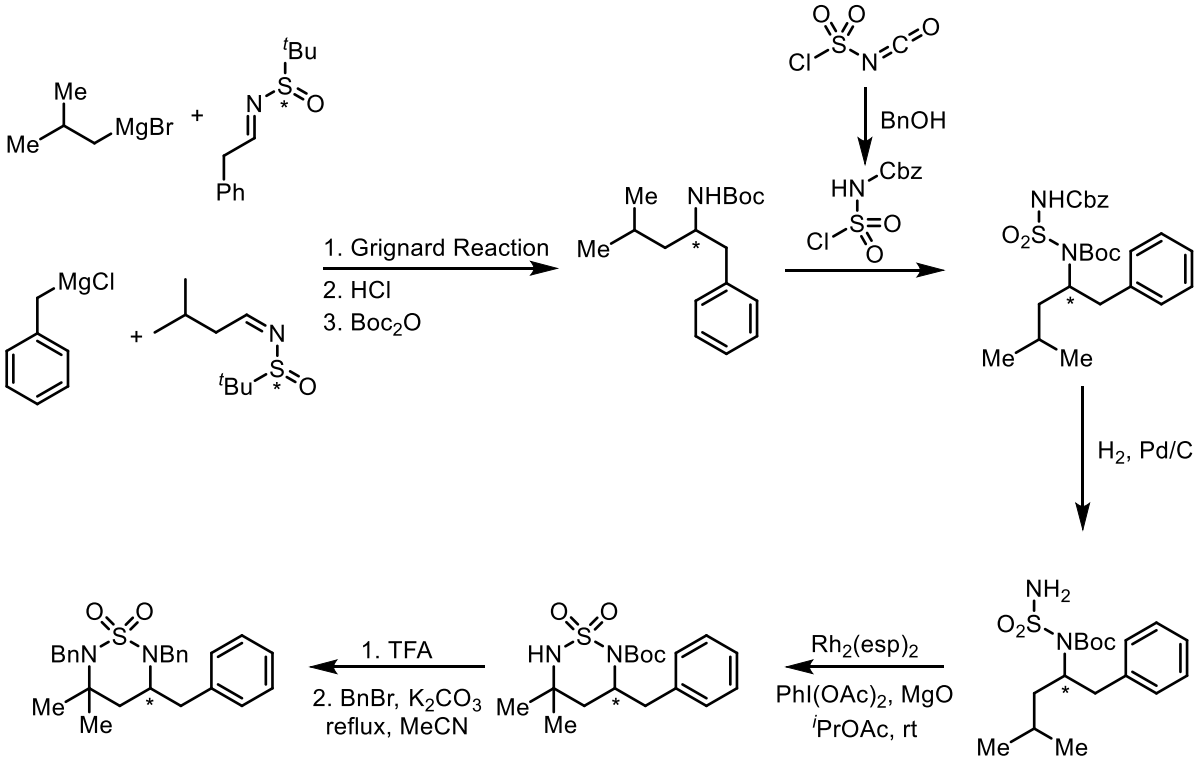
Moreover, efforts to cleave the sulfamide functional group have thus far proven unsuccessful (**Scheme 4.11**). Reaction of cyclic sulfamides in the presence of hydrobromic acid and phenol at elevated temperatures (which was successfully used in the deprotection of the 5-membered cyclic sulfamides) causes the starting material to decompose. Also, attempts to reduce the sulfamide functional group in refluxing lithium aluminum hydride leads to complete recovery of the starting material. Efforts are still underway to find a suitable means for accessing the 1,3-diamines while maintaining the enantiopurity of the compound.

Scheme 4.11 Efforts Towards the Deprotection to Afford 1,3-Diamines



The assignment of the absolute configuration of these compounds is currently under investigation. Current efforts are directed towards the use of Ellman's auxiliary to generate enantiopure *tert*-butyl (4-methyl-1-phenylpentan-2-yl)carbamate. We have successfully synthesized this compound by Grignard addition of benzyl magnesium chloride, but current levels of enantiopurity are unsatisfactory for determining absolute configuration. Grignard addition of isobutylmagnesium bromide should provide better levels of enantiopurity. Then, sulfonylation followed by selective removal of the Cbz group under reductive conditions should provide the sulfamide needed for the Rh-catalyzed C-H activation cyclization reaction. After successful cyclization, the boc group will be removed followed by alkylation to give the authentic sample.

Scheme 4.12 Proposed Synthesis of Authentic Sample for Determining Absolute Configuration of 6-membered Cyclic Sulfamides

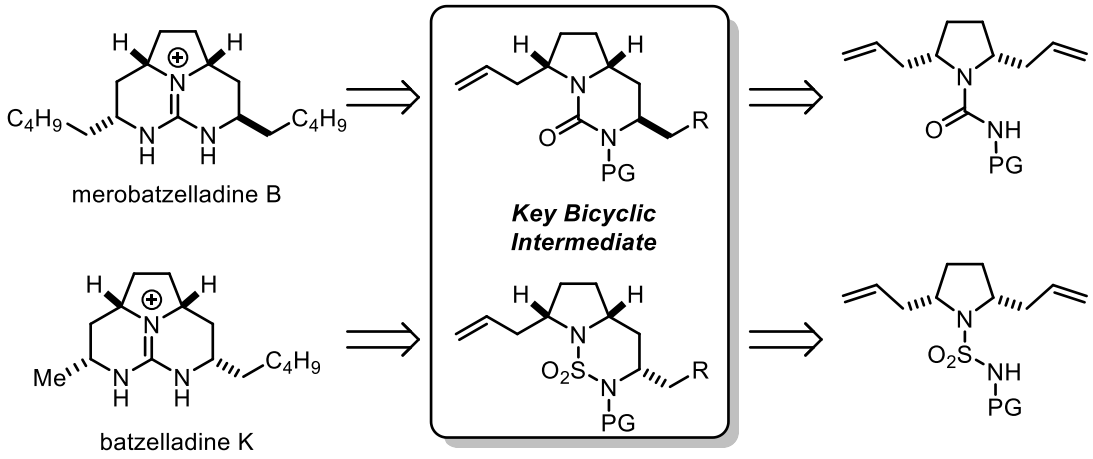


4.9 Desymmetrization of *Meso*-2,5-Diallylpyrrolidinyl Sulfamides for the Synthesis of Bicyclic Sulfamides

As described in chapter 3 and shown retrosynthetically in **Figure 4.2**, a key bicyclic intermediate is pivotal in the retrosynthesis of the batzelladine alkaloids. The synthesis of this key intermediate either through the use of ureas or sulfamides in the Pd-catalyzed carboamination reaction can enable access to the whole family of batzelladine alkaloids by capitalizing on the divergent reactivity *syn* and *anti* aminopalladation mechanism. The synthesis of racemic bicyclic sulfamides was accomplished recently with hopes of applications en route to the batzelladine alkaloids.[8] In order to achieve an enantioselective synthesis of the batzelladine alkaloids bearing hydrogens on the same face, a desymmetrization strategy akin to a strategy devised by

Wolfe and coworkers[2b] was considered. This desymmetrization strategy would utilize *meso*-2,5-diallylpyrrolidinyl sulfamides as substrates and utilize conditions that facilitate *anti* aminopalladations pathways in order to access stereoselectively the bicyclic scaffold required for advancement to the natural products. Key to the success of this proposition was finding a chiral ligand which could bias the mechanistic pathway of the reaction *and* achieve high levels of enantio-induction.

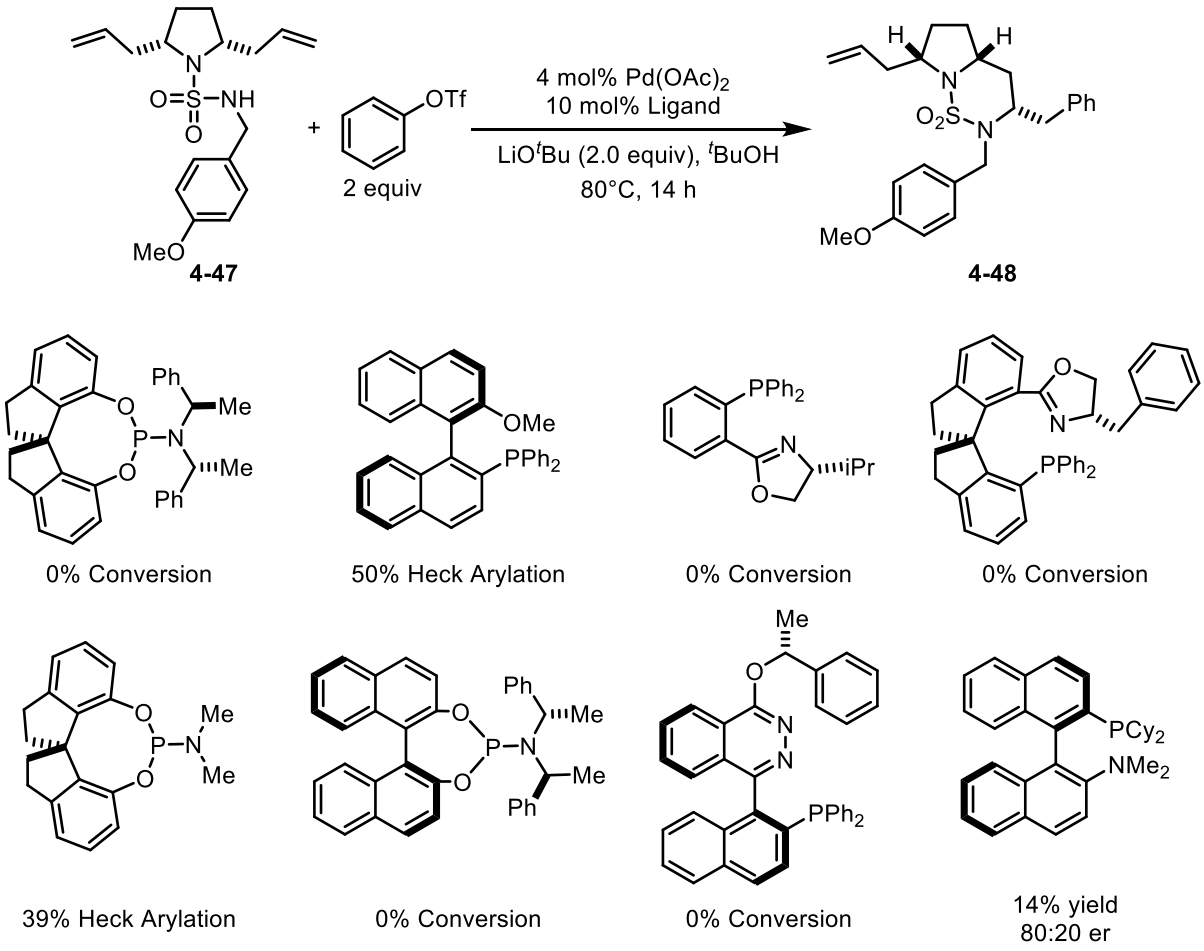
Figure 4.2 Batzelladine Alkaloids as Targets for Pd-Catalyzed Carboamination Reactions



Model substrate **4-47** was made in four steps with a sulfamide bearing a readily deprotected *p*-methoxybenzyl protecting group on the cyclizing nitrogen of the sulfamide. Then, evaluation of the carboamination reaction under *anti* aminopalladation conditions with phenyl triflate electrophile, lithium *tert* butoxide base and ^{t}BuOH solvent unveiled axially chiral Buchwald ligand KenPhos[9] as a potential scaffold for catalyst development. It is unsurprising that the other chiral ligands were unsuccessful in the

reaction because ligands that promote *anti* aminopalladation often bear electron-rich Buchwald ligands in order to promote the generation of the cationic palladium complex.

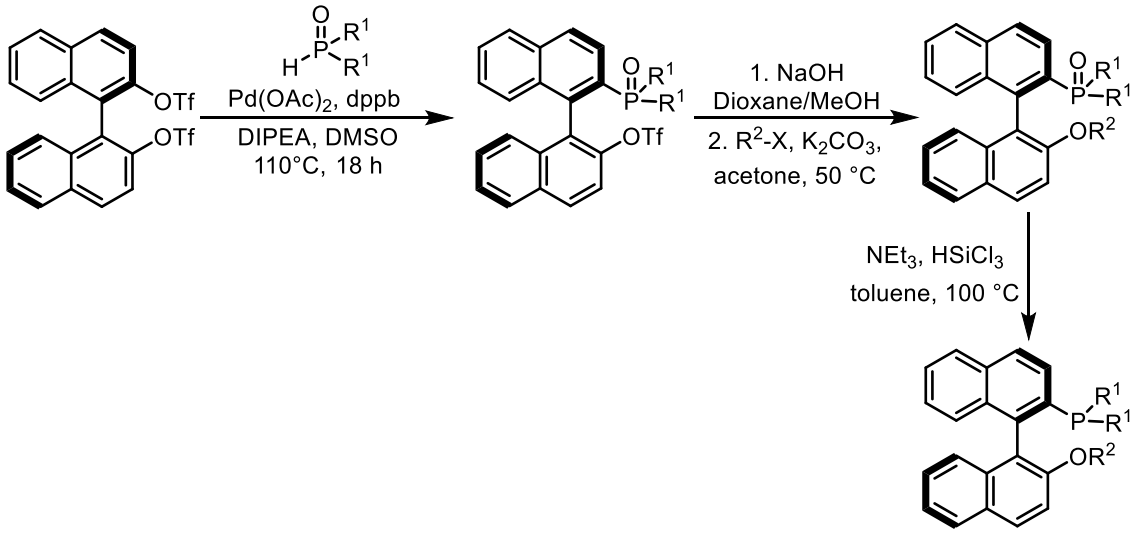
Scheme 4.13 Initial Screen of Chiral Ligands



While ligands like KenPhos are not commercially available, other groups have investigated their use in other asymmetric reactions like dearomative arylations of phenols,[10] arylation of imines,[11] arylation of ester enolates,[13a] and arylation of fluoroketones.[12b] This body of work describes a sequence for generating small libraries

of this ligand scaffold which can be utilized to pinpoint which aspects of the chiral ligand influence the enantioselectivity. This four step sequence begins by a Pd-catalyzed cross-coupling of the desired phosphine oxide with commercially available enantio-enriched [1,1'-binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate). Then, the triflate is hydrolyzed and alkylated. The new alkyl group at R^2 in **Scheme 4.14** often changes the enantioselectivity and thus serves as an accessible handle for testing new ligands. After alkylation, the phosphine oxide is reduced in the presence of trichlorosilane and triethylamine.

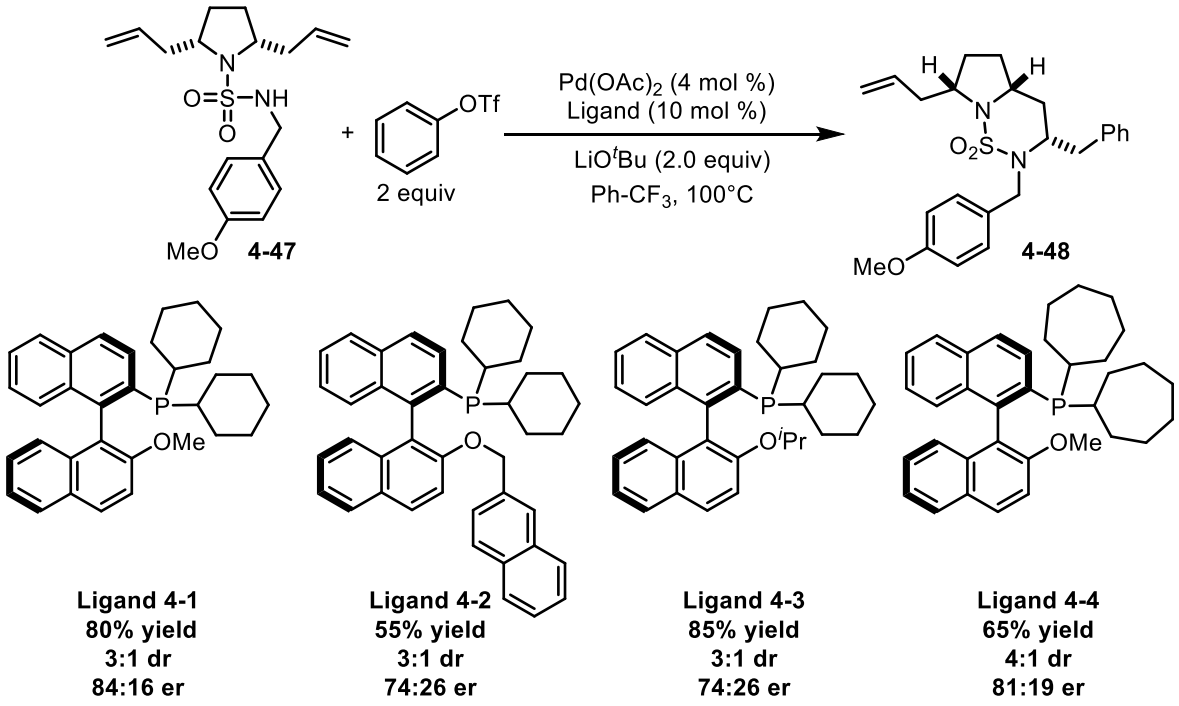
Scheme 4.14 Synthesis of Axially Chiral Buchwald Ligands



Using the route outlined above (**Scheme 4.14**), ligands that have been previously made in the literature were made and tested in the Pd-catalyzed carboamination reaction under *anti* aminopalladation conditions. Replacing the dimethylamino group of Kenphos with a methoxy group improved er (up to 84:16 er) and yield (up to 80%).

Unfortunately, further manipulations of the ligand scaffold failed to improve the enantioselectivity. This was somewhat disappointing as the examples from the literature demonstrate that increased steric bulk on the electron rich aryl ring improve enantioselectivity, whereas the products generated in **Scheme 4.15** were provided with diminished enantioselectivity as steric bulk of the ligand was increased.

Scheme 4.15 Enantioinduction via *Anti* Aminopalladation Pathways



Future work will investigate other manipulations of the chiral ligand scaffold. These manipulations might include changing the ligand backbone while maintaining the electron-rich phosphine. Also, further explorations of the reaction conditions may improve enantiomeric ratios to synthetically useful ratios. Finally, alterations of the protecting group on the cyclizing nitrogen may enhance the enantioselectivity.

4.10 Conclusion

This chapter describes the development of asymmetric methods towards the synthesis of chiral 1,2- and 1,3-diamines through Pd-catalyzed carboamination reactions of sulfamides. The reaction relies on commercially available ligand (*S*)-Siphos-PE to achieve high levels of enantioinduction. In addition, preliminary results have demonstrated the potential of axially chiral Buchwald ligands for developing enantio-induction under *anti* pathways. Further work in this area may unveil a chiral ligand or conditions which might achieve acceptable levels of enantioselectivity.

Future directions for this project should answer the following questions. What is the role of water in enhancing the product yield for the synthesis of 5-membered cyclic sulfamides? How can the monocyclic 6-membered cyclic sulfamides be deprotected without decomposing? What other protecting groups could be used to facilitate the asymmetric synthesis of the monocyclic 6-membered cyclic sulfamides? What ligands need to be developed for generating synthetically acceptable levels of enantioselectivity for the desymmetrization of *meso*-2,5-diallylpyrrolidinyl sulfamides? Is there erosion of enantioselectivity over time due to ligand decomposition under basic conditions? While the present work has not answered these questions, it is the hope of the author that future developments will be directed towards answering these questions.

A portion of the work described in this chapter was published in *Chemistry: A European Journal*.[13]

4.11 Experimental Section

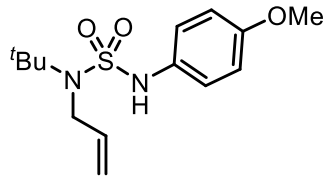
General: Reactions were carried out under nitrogen in flame-dried or oven-dried glassware unless otherwise specified. Tris(dibenzylideneacetone)dipalladium and (*S*)-SIPHOS-PE were purchased from Strem Chemical Co. and used without further purification. Dichloromethane and toluene were purified using a GlassContour solvent system. Xylenes were purified by distillation over CaH_2 prior to use in reactions. 1-Allyl-1,3-bisbenzylsulfamide[14] was prepared according to published procedures. All other solvents and aryl halides were purchased from commercial sources and used as received. Yields refer to isolated yields of compounds that are estimated to be $\geq$95% pure as judged by ^{1}H NMR or GC analysis. Unless otherwise noted, yields reported in **4.11 Experimental Section** describe the result of a single experiment, whereas yields reported in **Tables 4.2**, **Table 4.3** and **Table 4.4** are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those in the manuscript.

Synthesis of Substrates:

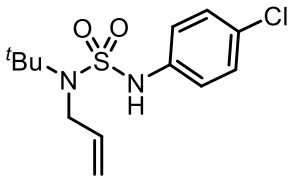
General procedure 1 for the synthesis of substrates:

A flame dried two neck round bottom flask equipped with a stir bar, condenser, and septum was cooled under a stream of nitrogen and charged with DMAP (0.20 equiv.) and oxazolidin-2-one substrate (1.0 equiv.). Anhydrous acetonitrile (5 mL/mmol) was added followed by triethylamine (3.0 equiv.). The reaction mixture was heated at 80 °C for 15 min, and then the allyl amine was added dropwise. The resulting mixture was

stirred for 16-18 h at 80 °C. The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant.

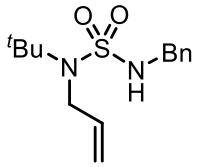


***N*-Allyl-*N'*-(4-methoxyphenyl)-*N*-*tert*-butylsulfamide.** General procedure 1 was used to sulfonylate *N*-(*tert*-butyl)prop-2-en-1-amine (1.2 g, 10.5 mmol) with 3-[(4-methoxyphenyl)sulfonyl]oxazolidin-2-one (2.6 g, 9.5 mmol) to afford the title compound (2.2 g, 79%) as a yellow solid, mp 77–81 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.11 (m, 2 H), 6.87–6.82 (m, 2 H), 6.22 (s, br, 1 H), 5.78 (m, 1 H), 5.12–5.06 (m, 1 H), 5.02 (dd, *J* = 10.3, 1.2 Hz, 1 H), 3.89 (dd, *J* = 6.0, 1.3 Hz, 2 H), 3.80 (s, 3 H), 1.40 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.6, 137.4, 130.1, 124.7, 116.9, 114.5, 59.7, 55.6, 50.1, 30.0; IR (neat) 3289, 2934, 1510, 1128 cm^{-1}; MS (ESI+) 299.1422 (299.1424 calcd for $C_{14}H_{22}N_2O_3S$, M + H+).

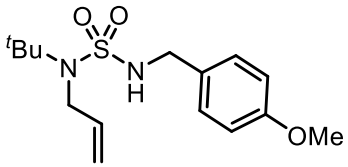


***N*-Allyl-*N'*-(4-chlorophenyl)-*N*-*tert*-butylsulfamide.** General procedure 1 was used to acylate *N*-(*tert*-butyl)prop-2-en-1-amine (1.2 g, 10.5 mmol) with 3-((4-chlorophenyl)sulfonyl)oxazolidin-2-one (2.6 g, 9.5 mmol) to afford the title compound

(2.0 g, 68%) as a colorless solid, mp 74–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.35 (m, 2 H), 7.04–7.14 (m, 2 H), 6.58 (s, 1 H), 5.71–5.84 (m, 1 H), 5.14 (dd, *J* = 17.2, 0.7 Hz, 1 H), 5.07 (dd, *J* = 10.3, 0.5 Hz, 1 H), 3.95 (d, *J* = 5.9 Hz, 2 H), 1.40 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 136.9, 136.1, 130.0, 129.5, 121.8, 116.9, 60.0, 50.1, 29.9; IR (neat) 3327, 3253, 2978, 1317, 1132 cm^{-1}; MS (ESI+) 325.0747 (325.0748 calcd for $C_{13}H_{19}ClN_2O_2S$, M + Na+).

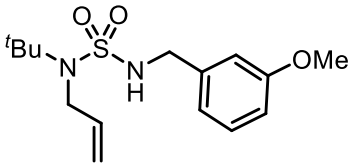


***N*-Allyl-*N'*-benzyl-*N*-*tert*-butylsulfamide.** General procedure 1 was used to sulfonylate *N*-(*tert*-butyl)prop-2-en-1-amine (3.1 mL, 20.9 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (4.87 g, 19 mmol) to afford the title compound (3.3 g, 61%) as a colorless solid. Spectra were identical to those previously reported.[15]

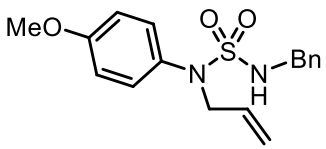


***N*-Allyl-*N'*-(4-methoxybenzyl)-*N*-*tert*-butylsulfamide.** General procedure 1 was used to sulfonylate *N*-(*tert*-butyl)prop-2-en-1-amine (1.2 g, 10.5 mmol) with 3-[(4-methoxybenzyl)sulfonyl]oxazolidin-2-one (2.7 g, 9.5 mmol) to afford the title compound (2.6 g, 87%) as a colorless solid, mp 66–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.22 (m, 2 H), 6.89–6.85 (m, 2 H), 6.03–5.92 (m, 1 H), 5.22 (dd, *J* = 17.4, 1.5 Hz, 1 H), 5.13

(dd, *J* = 10.3, 1.5 Hz, 1 H), 4.20–4.14 (m, 1 H), 4.08 (d, *J* = 6.1 Hz, 2 H), 3.95 (dt, *J* = 5.9, 1.4 Hz, 2 H), 3.80 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.5, 137.5, 129.6, 128.9, 116.6, 114.3, 59.4, 55.5, 49.5, 47.0, 29.9; IR (neat) 3325, 1513, 1313, 1248 cm^{-1}; MS (ESI+) 313.1581 (313.158 calcd for $C_{15}H_{24}N_2O_3S$, M + H+).

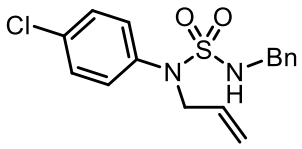


***N*-Allyl-*N'*-(3-methoxybenzyl)-*N*-*tert*-butylsulfamide.** General procedure 1 was used to sulfonylate *N*-(*tert*-butyl)prop-2-en-1-amine (1.2 g, 10.5 mmol) with 3-[(3-methoxybenzyl)sulfonyl]oxazolidin-2-one (2.7 g, 9.5 mmol) to afford the title compound (1.7 g, 58%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 1 H), 6.92–6.86 (m, 2 H), 6.83 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.02–5.92 (m, 1 H), 5.22 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.13 (dd, *J* = 10.3, 1.2 Hz, 1 H), 4.35 (t, *J* = 5.0 Hz, 1 H), 4.11 (d, *J* = 6.1 Hz, 2 H), 3.95 (dt, *J* = 6.0, 1.3 Hz, 2 H), 3.80 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.0, 138.5, 137.5, 129.9, 120.4, 116.7, 113.7, 113.6, 59.4, 55.4, 49.5, 47.4, 29.8; IR (neat) 3320, 3250, 1317, 1135 cm^{-1}; MS (ESI+) 313.1576 (313.158 calcd for $C_{15}H_{24}N_2O_3S$, M + H+).

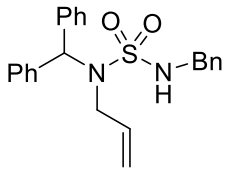


***N*-Allyl-*N'*-benzyl-*N*-(4-methoxyphenyl)sulfamide.** General procedure 1 was used to

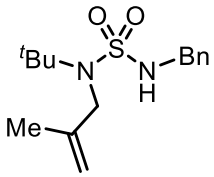
sulfonylate *N*-allyl-4-methoxyaniline (1.71 g, 10.5 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.5 g, 9.5 mmol) to afford the title compound (2.2 g, 70%) as a light brown solid, mp 58–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2 H), 7.31–7.27 (m, 3 H), 7.27–7.23 (m, 2 H), 6.89–6.85 (m, 2 H), 5.86–5.77 (m, 1 H), 5.13–5.10 (m, 1 H), 5.08 (t, *J* = 1.2 Hz, 1 H), 4.52 (t, *J* = 6.0 Hz, 1 H), 4.23 (d, *J* = 6.1 Hz, 2 H), 4.18 (dt, *J* = 6.5, 1.1 Hz, 2 H), 3.80 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.2, 136.8, 133.4, 132.8, 130.2, 128.9, 128.1, 128.1, 119.0, 114.5, 55.6, 55.3, 47.8; IR (neat) 3289, 1510, 1331, 1146 cm^{-1}; MS (ESI+) 333.1624 (333.1627 calcd for $C_{17}H_{20}N_2O_3S$, M + H+).



***N*-Allyl-*N'*-benzyl-*N*-(4-chlorophenyl)sulfamide.** General procedure 1 was used to sulfonylate *N*-allyl-4-chloroaniline (1.76 g, 10.5 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.5 g, 9.5 mmol) to afford the title compound (1.39 g, 43%) as a colorless solid, mp 61–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H), 7.28–7.22 (m, 4 H), 5.83–5.73 (m, 1 H), 5.12 (s, 1 H), 5.11–5.07 (m, 1 H), 4.58 (s, br, 1 H), 4.22 (d, *J* = 5.9 Hz, 2 H), 4.19 (dd, *J* = 6.5, 1.1 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.8, 136.6, 133.6, 133.0, 129.8, 129.5, 129.0, 128.3, 128.1, 119.4, 54.9, 47.8; IR (neat) 3294, 1488, 1338, 1145 cm^{-1}; MS (ESI+) 337.0769 (337.0772 calcd for $C_{16}H_{17}ClN_2O_2S$, M + H+).



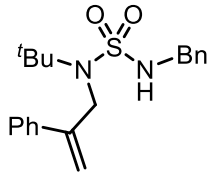
***N*-Allyl-*N*-benzhydryl-*N'*-benzylsulfamide.** General procedure 1 was used to sulfonylate *N*-benzhydrylprop-2-en-1-amine (1.52 g, 6.8 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (1.59 g, 6.2 mmol) to afford the title compound (1.2 g, 48%) as a colorless solid, mp 100–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 12 H), 7.19–7.15 (m, 2 H), 6.39 (s, 1 H), 5.40 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1 H), 4.98 (dd, *J* = 17.2, 1.3 Hz, 1 H), 4.92 (dd, *J* = 10.1, 1.1 Hz, 1 H), 4.23 (t, *J* = 6.0 Hz, 1 H), 4.05 (d, *J* = 6.1 Hz, 2 H), 3.95 (d, *J* = 6.4 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 139.5, 136.6, 134.6, 129.2, 128.9, 128.7, 128.2, 128.1, 128.0, 118.2, 65.9, 49.5, 47.4; IR (neat) 3300, 1433, 1324, 1142 cm^{-1}; MS (ESI+) 393.1628 (393.1631 calcd for $C_{23}H_{24}N_2O_2S$, M + H+).



***N'*-Benzyl-*N*-(*tert*-butyl)-*N*-(2-methylallyl)sulfamide.** A flame-dried round-bottom flask equipped with a stirbar and a septum was cooled under a stream of nitrogen and charged with *tert*-butylamine (6.3 mL, 60 mmol), 3-bromo-2-methylprop-1-ene (1.51, 15 mmol), and solid potassium carbonate (2.5 g, 18 mmol). The resulting mixture was stirred at rt for 24 h, then the mixture was filtered through celite. The celite was washed 3 x 20 mL diethyl ether. The organic layers were combined, and the solvent was removed under reduced pressure to afford crude *N*-(tert-butyl)-2-methylprop-2-en-1-amine (1.5 g, 80%) as a colorless oil which was carried on without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1 H), 4.79 (s, 1 H), 3.10 (s, 2 H), 1.77 (s, 3 H), 1.11 (s, 9 H)

General procedure 1 was used to sulfonylate *N*-(*tert*-butyl)-2-methylprop-2-en-1-amine (1.34 g, 10.5 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.5 g, 9.5 mmol) to afford the title compound (1.3 g, 47%) as a colorless solid, mp 76–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 5.07 (*d*, J = 0.7 Hz, 1 H), 4.93 (d, *J* = 1.2 Hz, 1 H), 4.21 (s, 3 H), 3.86 (s, 2 H), 1.77 (s, 3 H), 1.49–1.43 (m, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.0, 137.1, 128.9, 128.3, 128.1, 111.2, 59.6, 52.4, 47.8, 29.6, 20.5; IR (neat) 3327, 2977, 1321, 1133 cm^{-1}; MS (ESI+) 297.1629 (297.1631 calcd for $C_{15}H_{24}N_2O_2S$, M + H+).



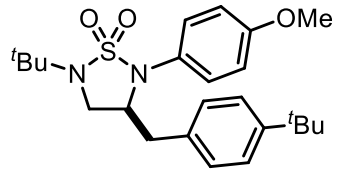
***N'*-Benzyl-*N*-(*tert*-butyl)-*N*-(2-phenylallyl)sulfamide.** The alkylation of *tert*-butylamine (6.3 mL, 60 mmol) with (3-bromoprop-1-en-2-yl)benzene (2.96 g, 15 mmol) in the presence of potassium carbonate (2.5 g, 18 mmol) was accomplished using a procedure analogous to that described above for the formation of **4a**. This procedure afforded *N*-(*tert*-butyl)-2-phenylprop-2-en-1-amine (2.4 g, 83%), which was carried on without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.3 Hz, 2 H), 7.37–7.31 (m, 2 H), 7,29 (d, *J* = 7.3 Hz, 1 H), 5.38 (s, 1 H), 5.28 (s, 1 H), 3.62 (s, 2 H), 1.15 (s, 9 H).

General procedure 1 was used to sulfonylate *N*-(*tert*-butyl)-2-phenylprop-2-en-1-

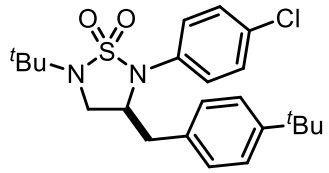
amine (2.0 g, 10.5 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.5 g, 9.5 mmol) to afford the title compound (2.4 g, 71%) as a colorless solid, mp 64–68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.25 (m, 10 H), 5.55–5.43 (m, 2 H), 4.31 (s, 2 H), 4.24–4.17 (m, 3 H), 1.53 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 146.7, 140.0, 137.0, 128.9, 128.6, 128.2, 128.1, 128.1, 126.4, 113.2, 59.9, 50.4, 47.9, 29.2; IR (neat) 3330, 2969, 1320, 1137 cm^{-1}; MS (ESI+) 359.1783 (359.1788 calcd for $C_{20}H_{26}N_2O_2S$, M + H+).

General procedure 2 for asymmetric Pd-catalyzed carboamination reactions.

An oven-dried test tube equipped with a stir bar and a rubber septum was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol %), *S*-SIPHOS-PE (5 mol %), the sulfamide substrate (1.0 equiv), and NaO^{t}Bu (2.0 equiv). The septum-capped tube was purged with N_2, and then the aryl or alkenyl halide (2.0 equiv), water (0 or 2.0 equiv.), and xylenes (0.125 M) were added. The resulting mixture was heated to 120 °C with stirring for 18 h. The reaction mixture was then cooled to rt and saturated aqueous ammonium chloride (6 mL/mmol substrate) was added. The mixture was extracted with ethyl acetate (3 x 2 mL) and then the combined organic layers were dried over anhydrous Na_2SO_4, filtered through a plug of celite, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant.

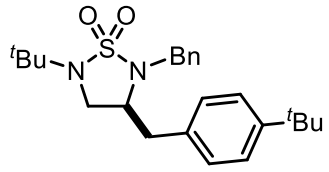


(–)-(*S*)-5-(*tert*-Butyl)-3-[4-(*tert*-butyl)benzyl]-2-(4-methoxyphenyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.1, entry 6). The general procedure 2 was employed for the coupling of *N*-allyl-*N'*-(4-methoxyphenyl)-*N*-*tert*-butylsulfamide (89.0 mg, 0.30 mmol) and 1-bromo-4-(*tert*-butyl)benzene (104 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (61 mg, 47%) as a yellow oil: $[\alpha]^{23}_D$ –21.5 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2 H), 7.32–7.28 (m, 2 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 6.96–6.92 (m, 2 H), 4.12–4.05 (m, 1 H), 3.82 (s, 3 H), 3.32 (dd, *J* = 8.7, 6.0 Hz, 1 H), 3.24–3.18 (m, 1 H), 2.95 (dd, *J* = 13.7, 4.2 Hz, 1 H), 2.63 (dd, *J* = 13.8, 9.8 Hz, 1 H), 1.42 (s, 9 H), 1.30 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 150.1, 132.9, 128.9, 128.7, 128.4, 125.8, 115.0, 57.4, 56.6, 55.7, 46.4, 38.0, 34.6, 31.5, 27.5; IR (neat) 2963, 1509, 1149 cm^{-1}; MS (ESI+) 431.2359 (431.2363 calcd for $C_{24}H_{34}N_2O_3S$, M + H^+). The enantiopurity was determined to be 81:19 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 7.2 and 9.9 min).



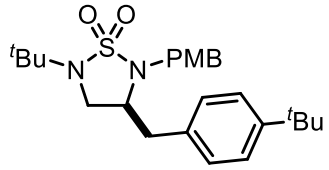
(–)-(*S*)-5-(*tert*-Butyl)-3-[4-(*tert*-butyl)benzyl]-2-(4-chlorophenyl)-1,2,5-thiadiazolidine 1,1-dioxide (Table 4.1, entry 7). The general procedure 2 was employed for the coupling of *N*-allyl-*N'*-(4-chlorophenyl)-*N*-*tert*-butylsulfamide (76.0 mg, 0.25 mmol) and

1-bromo-4-(*tert*-butyl)benzene (87 μL, 0.50 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (S)-SIPHOS-PE (7.6 mg, 0.015 mmol), sodium *tert*-butoxide (48.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (12 mg, 11%) yellow oil: $[\alpha]^{23}_D$ –10.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2 H), 7.30 (t, *J* = 7.9 Hz, 4 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 4.20–4.14 (m, 1 H), 3.36–3.40 (m, 1 H), 3.25 (t, *J* = 8.2 Hz, 1 H), 3.00 (dd, *J* = 13.9, 3.8 Hz, 1 H), 2.70 (dd, *J* = 13.8, 9.7 Hz, 1 H), 1.43 (s, 9 H), 1.31 (s, 9 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.3. 135.3, 132.7, 132.3, 129.8, 128.9, 125.9, 125.7, 57.0, 56.4, 46.0, 37.8, 34.7, 31.5, 27.6; IR (film) 2966, 1491, 1150 cm^{-1}. MS (ESI+) 435.1865 (435.1868 calcd for $C_{23}H_{31}ClN_2O_2S$, M + H^+). The enantiopurity was determined to be 73:27 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 10% IPA/Hexanes, 0.8 mL/min, λ 254 nm, RT= 8.8 and 18.0 min).



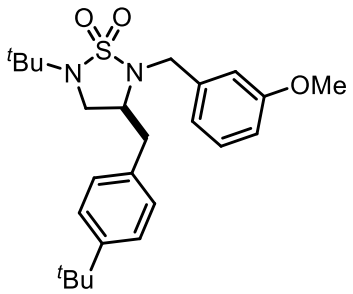
(–)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-[4-(*tert*-butyl)benzyl]-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.1, entry 5). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 1-bromo-4-(*tert*-butyl)benzene (104 μL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a

reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (112 mg, 90%) as a colorless solid, mp 114–118 °C: $[\alpha]^{23}_{D}$ –2.5 (*c* 10.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 2 H), 7.37–7.32 (m, 2 H), 7.31–7.23 (m, 3 H), 6.91 (d, *J* = 8.2 Hz, 2 H), 4.38 (d, *J* = 14.9 Hz, 1 H), 4.21 (d, *J* = 14.9 Hz, 1 H), 3.47–3.38 (m, 1 H), 3.18 (dd, *J* = 8.8, 6.5 Hz, 1 H), 3.06 (dd, *J* = 8.9, 6.2 Hz, 1 H), 2.93 (dd, *J* = 13.5, 4.3 Hz, 1 H), 2.61 (dd, *J* = 13.4, 10.1 Hz, 1 H), 1.40 (s, 9 H), 1.28 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 136.0, 133.5, 129.0, 128.8, 128.7, 128.0, 125.8, 56.6, 56.3, 50.0, 45.8, 38.0, 34.6, 31.5, 27.5; IR (neat) 2962, 1455, 1309, 1148 cm^{-1}; MS (ESI+) 437.2233 (437.2233 calcd for $C_{24}H_{34}N_2O_2S$, M + Na^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 205 nm, RT= 4.1 and 5.0 min).



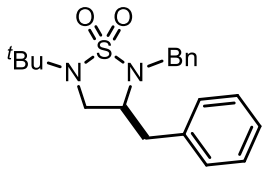
(–)-(*S*)-5-(*tert*-Butyl)-3-[4-(*tert*-butyl)benzyl]-2-(4-methoxybenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.1, entry 8). The general procedure 2 was employed for the coupling of *N*-allyl-*N'*-(4-methoxybenzyl)-*N*-*tert*-butylsulfamide (94.0 mg, 0.30 mmol) and 1-bromo-4-(*tert*-butyl)benzene (104 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (103 mg, 77%) as a colorless solid, mp 82–86 °C: $[\alpha]^{23}_{D}$ –9.6 (*c* 7.5, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2 H), 7.30–7.27 (m, 2 H), 6.94 (d, *J* = 8.3 Hz, 2 H), 6.90–6.86 (m, 2 H), 4.30 (d, *J* = 14.7 Hz, 1 H), 4.20 (d, *J* = 14.7 Hz, 1 H), 3.81 (s, 3 H), 3.46–3.39 (m, 1 H), 3.18 (dd, *J* = 8.9, 6.5 Hz, 1 H), 3.05 (dd, *J* = 8.9, 6.0 Hz, 1 H), 2.95 (dd, *J* = 13.5, 4.3 Hz, 1 H), 2.62 (dd, *J* = 13.4, 10.0 Hz, 1 H), 1.40 (s, 9 H), 1.30 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 150.0, 133.6, 130.4, 128.9, 127.8, 125.8, 114.3, 56.3, 56.2, 55.4, 49.4, 45.7, 38.0, 34.6, 31.5, 27.6; IR (neat) 2966, 1514, 1150 cm^{-1}; MS (ESI+) 445.2510 (445.2519 calcd for $C_{25}H_{36}N_2O_3S$, M + H^+). The enantiopurity was determined to be 91:9 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 215 nm, RT= 5.0 and 6.2 min).



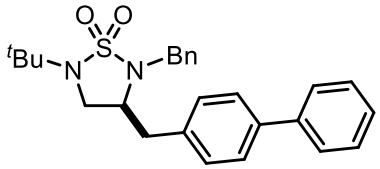
(–)-(*S*)-5-(*tert*-Butyl)-3-[4-(*tert*-butyl)benzyl]-2-(3-methoxybenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.1, entry 10). The general procedure 2 was employed for the coupling of *N*-allyl-*N'*-(3-methoxybenzyl)-*N*-*tert*-butylsulfamide (94.0 mg, 0.30 mmol) and 1-bromo-4-(tert-butyl)benzene (104 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (80 mg, 60%) as a yellow oil: $[\alpha]^{23}_D$ –4.4 (*c* 6.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.22 (m, 3 H), 7.00–6.92 (m, 2 H), 6.92 (d, *J* = 8.2 Hz, 2 H), 6.85–6.81

(m, 1 H), 4.35 (d, *J* = 14.7 Hz, 1 H), 4.18 (d, *J* = 14.7 Hz, 1 H), 3.80 (s, 3 H), 3.47–3.39 (m, 1 H), 3.18 (dd, *J* = 8.8, 6.5 Hz, 1 H), 3.05 (dd, *J* = 8.9, 6.2 Hz, 1 H), 2.93 (dd, *J* = 13.5, 4.3 Hz, 1 H), 2.61 (dd, *J* = 13.4, 10.1 Hz, 1 H), 1.39 (s, 9 H), 1.27 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 150.0, 137.6, 133.5, 129.7, 128.9, 125.8, 121.2, 114.2, 113.8, 56.6, 56.3, 55.4, 50.0, 45.8, 37.9, 34.6, 31.5, 27.3; IR (neat) 2963, 1600, 1150 cm^{-1}; MS (ESI+) 445.2513 (445.2519 calcd for $C_{25}H_{36}N_2O_3S$, M + H^+). The enantiopurity was determined to be 91:9 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 230 nm, RT= 5.2 and 7.3 min).



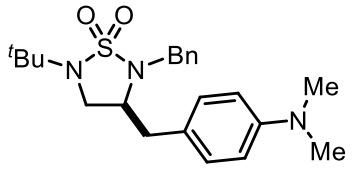
(–)-(*S*)-2,3-Dibenzyl-5-(*tert*-butyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 1). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and bromobenzene (63 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 µL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (101 mg, 94%) as a colorless solid, mp 108–111 °C: $[\alpha]^{23}_D$ –8.5 (*c* 4.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.33–7.19 (m, 4 H), 7.00 (d, *J* = 7.3 Hz, 2 H), 4.39 (d, *J* = 14.7 Hz, 1 H), 4.22 (d, *J* = 15.2 Hz, 1 H), 3.49–3.42 (m, 1 H), 3.19–3.13 (m, 1 H), 3.05 (dd, *J* = 8.1, 7.1 Hz, 1 H), 2.98 (dd, *J* = 13.7, 4.4 Hz, 1 H), 2.64 (dd, *J* = 13.2, 10.3 Hz, 1 H),

1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 136.0, 129.2, 129.0, 128.9, 128.8, 128.1, 127.1, 56.6, 56.4, 50.1, 45.7, 38.6, 27.5; IR (neat) 2962, 1314, 1150 cm^{-1}; MS (ESI+) 381.1607 (381.1607 calcd for $C_{20}H_{26}N_2O_2S$, M + Na^+). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 4% IPA/Hexanes, 0.5 mL/min, λ 210 nm, RT= 18.6 and 20.7 min).



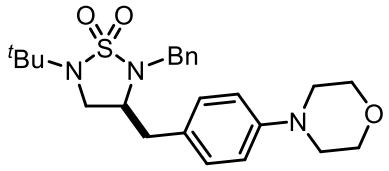
(+)-(*S*)-3-[(1,1'-Biphenyl)-4-ylmethyl]-2-benzyl-5-(*tert*-butyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 3). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 4-bromobiphenyl (140.0 mg, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (122 mg, 94%) as a colorless solid, mp 109–113 °C: $[\alpha]^{23}_D$ +0.51 (*c* 3.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.46–7.41 (m, 4 H), 7.40–7.30 (m, 4 H), 7.08 (d, *J* = 8.1 Hz, 2 H), 4.43 (d, *J* = 14.9 Hz, 1 H), 4.24 (d, *J* = 14.9 Hz, 1 H), 3.51 (d, *J* = 5.1 Hz, 1 H), 3.23 (dd, *J* = 8.9, 6.5 Hz, 1 H), 3.10 (dd, *J* = 8.8, 6.1 Hz, 1 H), 3.03 (dd, *J* = 13.4, 4.6 Hz, 1 H), 2.70 (dd, *J* = 13.4, 10.0 Hz, 1 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.0, 136.0, 135.6, 129.6, 129.0, 129.0, 128.8, 128.1, 127.6, 127.5, 127.1, 56.6, 56.4, 50.2, 45.8, 38.3, 27.6; IR (neat) 2974,

1487, 1311, 1151 cm^{-1}; MS (ESI+) 435.2094 (435.2101 calcd for $C_{26}H_{30}N_2O_2S$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 14.8 and 24.7 min).



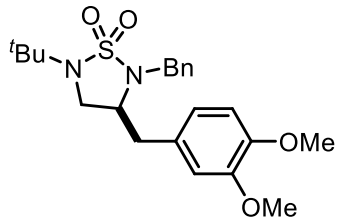
(+)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-[4-(dimethylamino)benzyl]-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 5). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 4-bromo-*N,N*-dimethylaniline (120.0 mg, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (91 mg, 76%) as a red solid, mp 118–122 °C: $[\alpha]^{23}_D$ +17.3 (*c* 5.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 2 H), 7.37 (t, *J* = 7.7 Hz, 2 H), 7.34–7.29 (m, 1 H), 6.88 (d, *J* = 8.1 Hz, 2 H), 6.64 (d, *J* = 7.8 Hz, 2 H), 4.42 (d, *J* = 14.9 Hz, 1 H), 4.23 (d, *J* = 15.1 Hz, 1 H), 3.40 (d, *J* = 5.9 Hz, 1 H), 3.17 (dd, *J* = 8.2, 7.2 Hz, 1 H), 3.04–3.10 (m, 1 H), 2.88–2.95 (m, 7 H), 2.54 (dd, *J* = 13.3, 10.4 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 136.2, 129.8, 128.9, 128.7, 128.0, 124.0, 113.0, 57.0, 56.3, 49.9, 45.8, 40.8, 37.6, 27.5; IR (neat) 2900, 1615, 1524, 1303 cm^{-1}; MS (ESI+) 402.2206 (402.2210 calcd for $C_{22}H_{31}N_3O_2S$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00

mL/min, λ 254 nm, RT= 7.4 and 9.5 min).

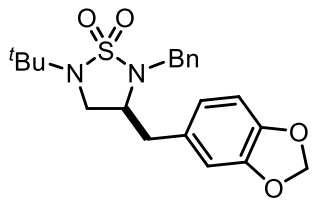


(–)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-(4-morpholinobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 6). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 4-(4-bromophenyl)morpholine (145.0 mg, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (S)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (105 mg, 79%) as a yellow solid, mp 95–99 °C: $[\alpha]^{23}_D$ –11.5 (*c* 5.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2 H), 7.38–7.33 (m, 2 H), 7.31 (d, *J* = 7.1 Hz, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 4.40 (d, *J* = 14.9 Hz, 1 H), 4.20 (d, *J* = 14.9 Hz, 1 H), 3.87–3.82 (m, 4 H), 3.40 (d, *J* = 5.6 Hz, 1 H), 3.15 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.13–3.09 (m, 4 H), 3.03 (dd, *J* = 8.9, 6.5 Hz, 1 H), 2.91 (dd, *J* = 13.6, 4.5 Hz, 1 H), 2.56 (dd, *J* = 13.4, 10.0 Hz, 1 H), 1.39 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 136.1, 129.9, 129.0, 128.7, 128.0, 127.7, 116.1, 67.0, 56.8, 56.3, 50.1, 49.5, 45.8, 37.7, 27.5; IR (neat) 2814, 1598, 1516, 1151 cm^{-1}; MS (ESI+) 444.2311 (444.2315 calcd for $C_{24}H_{33}N_3O_3S$, M + H$^+$). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00

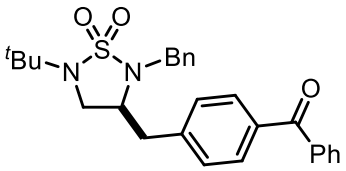
mL/min, λ 254 nm, RT= 18.2 and 22.6 min).



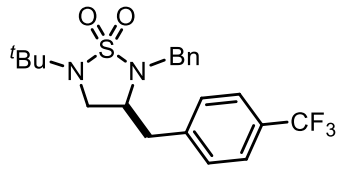
(–)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-(3,4-dimethoxybenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 7). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 4-bromo-1,2-dimethoxybenzene (86 μL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (99 mg, 79%) as a yellow oil: $[\alpha]^{23}_D$ –5.8 (*c* 5.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2 H), 7.36–7.23 (m, 3 H), 6.73 (d, *J* = 8.2 Hz, 1 H), 6.54 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.42 (d, *J* = 1.8 Hz, 1 H), 4.36 (d, *J* = 14.9 Hz, 1 H), 4.18 (d, *J* = 14.9 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.44–3.36 (m, 1 H), 3.16 (dd, *J* = 8.8, 6.5 Hz, 1 H), 3.02 (dd, *J* = 8.9, 6.2 Hz, 1 H), 2.90 (dd, *J* = 13.4, 4.6 Hz, 1 H), 2.56 (dd, *J* = 13.5, 9.6 Hz, 1 H), 1.38 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 148.1, 136.0, 129.1, 129.0, 128.7, 128.0, 121.2, 112.2, 111.5, 56.7, 56.3, 56.1, 56.0, 50.2, 45.8, 38.3, 27.5; IR (neat) 2976, 1661, 1514, 1150 cm^{-1}; MS (ESI+) 419.1997 (419.1999 calcd for $C_{22}H_{30}N_2O_4S$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 233 nm, RT= 15.1 and 20.8 min).



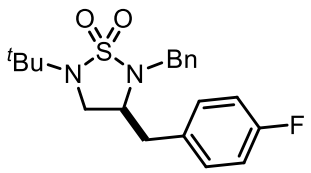
(–)-(*S*)-3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-benzyl-5-(*tert*-butyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 12). The general procedure 2 was employed for the coupling of *N*-Allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 5-bromobenzo[*d*][1,3]dioxole (72 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 µL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (88 mg, 73%) as a colorless solid, mp 99–102 °C: $[\alpha]^{23}_D$ –14.2 (*c* 4.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.31 (d, *J* = 7.3 Hz, 1 H), 6.69 (d, *J* = 7.8 Hz, 1 H), 6.48–6.42 (m, 2 H), 5.92 (s, 2 H), 4.40 (d, *J* = 14.9 Hz, 1 H), 4.19 (d, *J* = 14.9 Hz, 1 H), 3.42–3.34 (m, 1 H), 3.21–3.15 (m, 1 H), 3.03 (dd, *J* = 8.6, 6.4 Hz, 1 H), 2.88 (dd, *J* = 13.6, 4.5 Hz, 1 H), 2.54 (dd, *J* = 13.4, 10.0 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 146.7, 136.0, 130.2, 129.0, 128.8, 128.1, 122.2, 109.3, 108.7, 101.2, 56.8, 56.4, 50.3, 45.7, 38.4, 27.6; IR (neat) 2976, 1493, 1313, 1150 cm^{-1}; MS (ESI+) 403.1688 (403.1686 calcd for $C_{21}H_{26}N_2O_4S$, M + H^+). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 10% IPA/Hexanes, 1.00 mL/min, λ 280 nm, RT= 7.0 and 11.6 min).



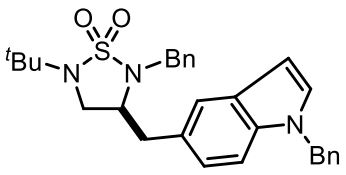
(–)-(S)-(4-{[2-benzyl-5-(*tert*-butyl)-1,1-dioxido-1,2,5-thiadiazolidin-3-yl]methyl}phenyl)(phenyl)methanone (Table 4.2, entry 8). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 4-bromobenzophenone (157 mg, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (106 mg, 76%) as a colorless solid, mp 119–121 °C: $[\alpha]^{23}_D$ –3.3 (*c* 10.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.1, 1.2 Hz, 2 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 7.61–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 7.42–7.38 (m, 2 H), 7.37–7.28 (m, 3 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 4.40 (d, *J* = 14.9 Hz, 1 H), 4.21 (d, *J* = 14.9 Hz, 1 H), 3.51 (d, *J* = 4.4 Hz, 1 H), 3.23 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.08–3.02 (m, 2 H), 2.75 (dd, *J* = 13.4, 9.5 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 141.5, 137.6, 136.4, 135.7, 132.6, 130.7, 130.1, 129.2, 128.9, 128.8, 128.4, 128.1, 56.4, 56.3, 50.5, 45.7, 38.7, 27.5; IR (neat) 2976, 1661, 1311, 1151 cm^{-1}; MS (ESI+) 463.2048 (463.2050 calcd for $C_{27}H_{30}N_2O_3S$, M + H^+). The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 32.7 and 68.3 min).



(–)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-[4-(trifluoromethyl)benzyl]-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 9). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 4-bromobenzotrifluoride (84 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 µL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (95 mg, 74%) as a colorless solid, mp 139–142 °C: $[\alpha]^{23}_D$ –16.5 (*c* 8.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2 H), 7.37–7.28 (m, 5 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 4.39 (d, *J* = 14.7 Hz, 1 H), 4.17 (d, *J* = 14.7 Hz, 1 H), 3.50–3.43 (m, 1 H), 3.23 (dd, *J* = 9.0, 6.6 Hz, 1 H), 3.05–2.99 (m, 2 H), 2.72 (dd, *J* = 13.4, 9.3 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 135.7, 129.6, 129.6 (q, *J* = 65.4 Hz), 129.0, 128.8, 128.2, 125.8 (q, *J* = 3.77 Hz), 124.2 (q, *J* = 271.6 Hz), 56.4, 56.3, 50.8, 45.8, 38.7, 27.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.56; IR (neat) 2975, 1314, 1152 cm^{-1}; MS (ESI+) 427.1660 (427.1662 calcd for $C_{21}H_{25}F_3N_2O_2S$, M + H^+). The enantiopurity was determined to be 88:12 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 6.0 and 8.3 min).

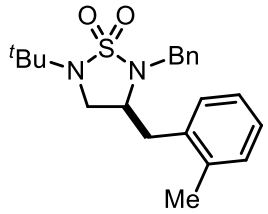


(–)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-(4-fluorobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 10). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 1-bromo-4-fluorobenzene (66 μL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (81 mg, 72%) as a colorless solid, mp 100–102 °C: $[\alpha]^{23}_D$ –15.6 (*c* 7.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 2 H), 7.35 (t, *J* = 7.2 Hz, 2 H), 7.31 (d, *J* = 7.1 Hz, 1 H), 6.97–6.92 (m, 4 H), 4.38 (d, *J* = 14.7 Hz, 1 H), 4.18 (d, *J* = 14.9 Hz, 1 H), 3.45–3.38 (m, 1 H), 3.18 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.02 (dd, *J* = 8.8, 6.1 Hz, 1 H), 2.94 (dd, *J* = 13.7, 4.9 Hz, 1 H), 2.62 (dd, *J* = 13.6, 9.7 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (d, *J* = 246.5 Hz), 135.9, 132.3 (d, *J* = 2.5 Hz), 130.7 (d, *J* = 8.8 Hz), 128.9 (d, *J* = 18.9 Hz), 128.1, 115.9, 115.7, 56.6, 56.4, 50.4, 45.7, 38.0, 27.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ□–115.7; IR (neat) 2974, 1509, 1315, 1152 cm^{-1}; MS (ESI+) 377.1694 (377.1694 calcd for $C_{20}H_{25}FN_2O_2S$, M + H^+). The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 220 nm, RT= 6.1 and 10.5 min).



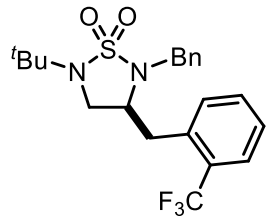
(–)-(*S*)-2-Benzyl-3-[(1-benzyl-1*H*-indol-6-yl)methyl]-5-(*tert*-butyl)-1,2,5-

thiadiazolidine-1,1-dioxide (Table 4.2, entry 11). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 1-benzyl-5-bromo-1*H*-indole (172.0 mg, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (122 mg, 83%) as a colorless solid, mp 158–161 °C: $[\alpha]^{23}_D$ – 1.6 (*c* 8.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 2 H), 7.40–7.34 (m, 2 H), 7.34–7.25 (m, 5 H), 7.20–7.09 (m, 4 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 5.31 (s, 2 H), 4.44 (d, *J* = 14.9 Hz, 1 H), 4.26 (d, *J* = 14.9 Hz, 1 H), 3.55–3.48 (m, 1 H), 3.19–3.08 (m, 3 H), 2.72 (dd, *J* = 13.3, 10.4 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 136.2, 135.5, 129.2, 129.0, 129.0, 128.9, 128.7, 128.0, 127.8, 127.5, 126.9, 123.0, 121.3, 110.1, 101.5, 57.2, 56.3, 50.4, 50.0, 45.8, 38.7, 27.6; IR (neat) 2974, 1314, 1152 cm^{-1}; MS (ESI+) 488.2366 (488.2366 calcd for $C_{29}H_{33}N_3O_2S$, M + H^+). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 220 nm, RT= 31.9 and 74.6 min).



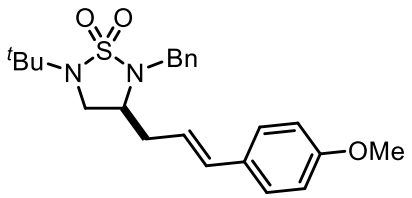
(+)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-(2-methylbenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 16). The general procedure 2 was employed for the coupling of *N*-

allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 2-bromotoluene (72 μL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (61 mg, 54%) as a colorless solid, mp 75–78 °C: $[\alpha]^{23}_D$ +19.3 (*c* 4.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2 H), 7.37–7.32 (m, 2 H), 7.30 (d, *J* = 6.8 Hz, 1 H), 7.15–7.07 (m, 3 H), 6.99 (d, *J* = 6.8 Hz, 1 H), 4.40–4.34 (m, 1 H), 4.27–4.21 (m, 1 H), 3.51–3.43 (m, 1 H), 3.20–3.14 (m, 1 H), 3.10 (dd, *J* = 8.8, 5.9 Hz, 1 H), 3.02 (dd, *J* = 13.6, 4.5 Hz, 1 H), 2.69 (dd, *J* = 13.6, 10.1 Hz, 1 H), 2.05 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 136.0, 134.9, 130.8, 130.2, 128.9, 128.8, 128.1, 127.3, 126.3, 56.4, 54.9, 50.1, 45.8, 36.1, 27.6, 19.4; IR (neat) 2977, 1290, 1148 cm^{-1}; MS (ESI+) 373.1946 (373.1944 calcd for $C_{21}H_{28}N_2O_2S$, M + H^+). The enantiopurity was determined to be 68:32 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 1.00 mL/min, λ 225 nm, RT= 6.5 and 7.7 min).



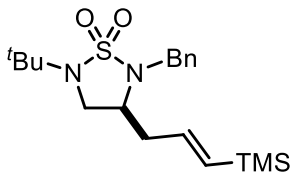
(+)-(*S*)-2-Benzyl-5-(*tert*-butyl)-3-[2-(trifluoromethyl)benzyl]-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 15). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and 2-

bromobenzotrifluoride (82 µL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 µL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (30 mg, 23%) as a yellow oil: $[\alpha]^{23}_D$ +18.2 (*c* 4.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1 H), 7.48–7.42 (m, 1 H), 7.38–7.32 (m, 1 H), 7.31–7.22 (m, 6 H), 4.33 (d, *J* = 14.9 Hz, 1 H), 4.14 (d, *J* = 14.9 Hz, 1 H), 3.63–3.54 (m, 1 H), 3.28–3.19 (m, 2 H), 3.10 (dd, *J* = 8.9, 5.7 Hz, 1 H), 2.91–2.84 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 135.1, 132.8, 132.0, 128.9, 128.9 (q, *J* = 28.8 Hz), 128.7, 127.9, 127.3, 126.6 (q, *J* = 4.4 Hz), 124.5 (q, *J* = 273.8 Hz), 56.4, 56.0, 51.3, 46.1, 36.1, 27.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ –59.4; IR (neat) 2978, 1312, 1150, 1113 cm^{-1}; MS (ESI+) 427.1664 (427.1662 calcd for $C_{21}H_{25}F_3N_2O_2S$, M + H^+). The enantiopurity was determined to be 62:38 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 230 nm, RT= 3.6 and 5.7 min).



(+)-(*S,E*)-2-Benzyl-5-(*tert*-butyl)-3-[3-(4-methoxyphenyl)allyl]-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 13). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and (*E*)-1-(2-bromovinyl)-4-methoxybenzene (128 mg, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11

μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title compound (56 mg, 45%) as a yellow oil: $[\alpha]^{23}_{D}$ +31.6 (*c* 4.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2 H), 7.37–7.31 (m, 2 H), 7.29 (d, *J* = 7.3 Hz, 1 H), 7.22 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 5.84–5.77 (m, 1 H), 4.48 (d, *J* = 15.2 Hz, 1 H), 4.13 (d, *J* = 15.2 Hz, 1 H), 3.80 (s, 3 H), 3.42–3.36 (m, 2 H), 3.15–3.08 (m, 1 H), 2.51–2.43 (m, 1 H), 2.35–2.27 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 136.3, 133.3, 129.8, 128.8, 128.7, 128.0, 127.5, 121.5, 114.2, 56.4, 55.6, 55.5, 50.2, 45.8, 36.2, 27.5; IR (neat) 2975, 1606, 1510, 1246, 1148 cm^{-1}; MS (ESI+) 415.2050 (415.205 calcd for $C_{23}H_{30}N_2O_3S$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 13.5 and 26.3 min).

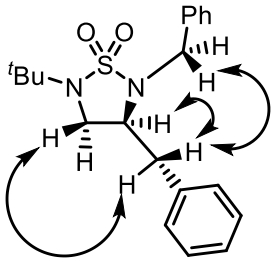


(+)-(*S,E*)-2-Benzyl-5-(*tert*-butyl)-3-[3-(trimethylsilyl)allyl]-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.2, entry 14). The general procedure 2 was employed for the coupling of *N*-allyl-*N*'-benzyl-*N*-*tert*-butylsulfamide (85.0 mg, 0.30 mmol) and (*E*)-(2-bromovinyl)trimethylsilane (92 μL, 0.60 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and (*S*)-SIPHOS-PE (7.6 mg, 0.015 mmol), water (11 μL, 0.60 mmol), sodium *tert*-butoxide (58.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.4 mL of xylenes. This procedure afforded the title

compound (46 mg, 40%) as a yellow oil: $[\alpha]^{23}_{D}$ +22.3 (*c* 2.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.1 Hz, 2 H), 7.36–7.31 (m, 2 H), 7.28 (d, *J* = 7.3 Hz, 1 H), 5.82–5.67 (m, 2 H), 4.42 (d, *J* = 15.2 Hz, 1 H), 4.10 (d, *J* = 15.2 Hz, 1 H), 3.39–3.30 (m, 2 H), 3.08–3.04 (m, 1 H), 2.43–2.37 (m, 1 H), 2.28–2.21 (m, 1 H), 1.42 (s, 9 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 136.3, 135.9, 128.7, 128.7, 127.9, 56.4, 55.0, 50.0, 45.6, 39.6, 27.5, –1.2; IR (neat) 2954, 1617, 1293, 1247, 1149 cm^{-1}; MS (ESI+) 381.2029 (381.2027 calcd for $C_{19}H_{32}N_2O_2SSi$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 220 nm, RT= 2.9 and 7.5 min).

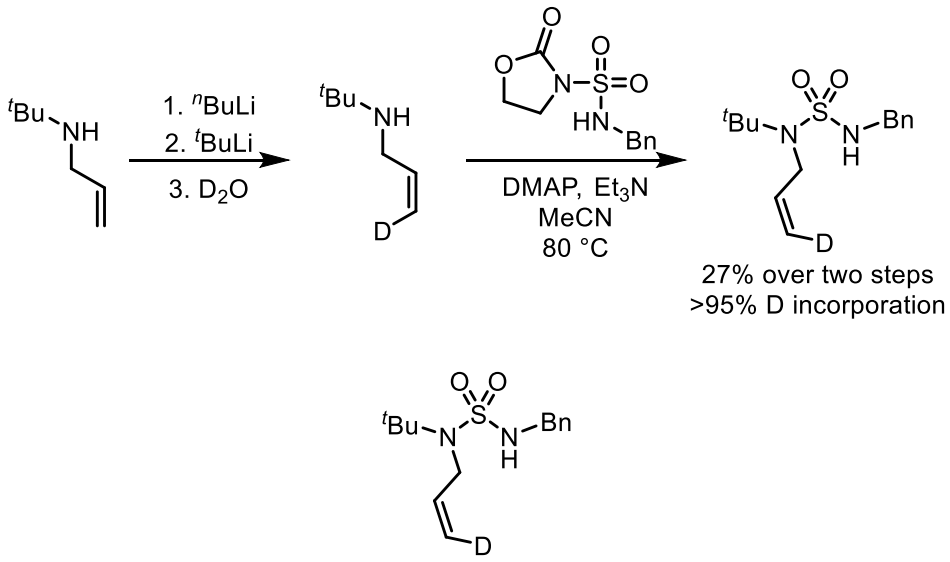
Deuterium Labeling Studies

The configuration of deuterated products were assigned on the basis of 1D NOESY experiments carried out with the all-proteo analogs of these compounds. The key nOe signals are shown below.



The configuration of the deuterated products was then assigned by examining which signal was absent from the ^{1}H NMR.

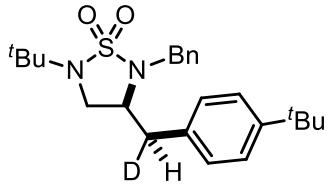
Reaction Sequence for Deuterium Labeled Substrate



(*Z*)-1-(3-*d*-Allyl)-1-benzyl-3-*tert*-butylsulfamide (4-21). The procedure previously described by our group for the preparation of (*Z*)-1-(3-*d*-Allyl)-1,3-dibenzylsulfamide was used for the synthesis of **8**.[15,16] A flame dried round bottom flask equipped with a stir bar was cooled to rt under a stream of nitrogen and charged with *N*-(*tert*-butyl)prop-2-en-1-amine (10.0 mmol, 1.13 g) and Et_2O (20 mL). The resulting solution was cooled to –42 °C using a CO_2/CH_3CN bath and stirred for 5 min. A solution of *n*-BuLi in hexanes (4.8 mL, 2.5 M, 12 mmol) was added slowly, and the resulting mixture was stirred at –42 °C for 20 min. A solution of *t*-BuLi in pentanes (13.0 mL, 1.7 M, 22 mmol) was added slowly and the resulting solution was stirred at –42 °C for 30 min. The CO_2/CH_3CN bath was replaced with a brine/ice bath, and the reaction mixture was allowed to slowly warm to rt as the ice melted. The bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was then cooled to –78 °C, and D_2O (3.6 mL, 200 mmol) was added dropwise. The resulting mixture was warmed to rt and stirred overnight. The reaction mixture was cooled to 0 °C, quenched with H_2O (15 mL) and transferred to a separatory funnel. The mixture was extracted with Et_2O (3 x 10 mL). The combined

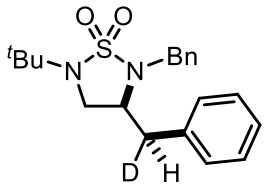
organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield crude (*Z*)-*N*-(*tert*-butyl)prop-2-en-3-d-1-amine.

A flame dried two necked flask equipped with stir bar and condenser was then charged with *N*-benzyl-2-oxooxazolidine-3-sulfonamide (2.56 g, 10 mmol), 4-dimethylaminopyridine (244 mg, 2 mmol), acetonitrile (50mL) and Et_3N (4.2 mL, 30 mmol). The reaction vessel was placed in an oil bath at 80 ºC and the mixture was stirred for 15 min. Neat (*Z*)-*N*-(*tert*-butyl)prop-2-en-3-d-1-amine was added, and the resulting mixture was stirred at 80 °C for ca. 6 h. The mixture was cooled to rt, and the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant to yield 770 mg (27%) of a yellow solid, mp 73–75 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5 H), 6.01–5.91 (m, 1 H), 5.12 (d, *J* = 10.3 Hz, 1 H), 4.27–4.19 (m, 1 H), 4.15 (d, *J* = 6.1 Hz, 2 H), 3.96 (dd, *J* = 6.0, 1.1 Hz, 2 H), 1.47 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 136.9, 128.9, 128.3, 128.1, 116.5 (t, *J* = 23.9 Hz), 59.4, 49.5, 47.5, 29.9; IR (neat) 3328, 2970, 1317, 1137 cm^{-1}; MS (ESI+) 306.1358 (306.1357 calcd for $C_{14}H_{21}DN_2O_2S$, M + Na^+).



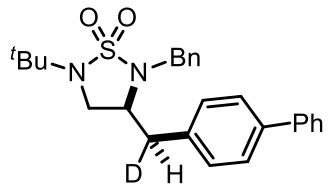
(–)-(1'*R*,3*S*)-2-Benzyl-5-(*tert*-butyl)-3-{[4-(*tert*-butyl)phenyl]methyl-d}-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.3, entry 1). The general procedure 2 was employed for the coupling of (*Z*)-1-(3-*d*-allyl)-1-benzyl-3-*tert*-butylsulfamide (71.0 mg,

0.25 mmol) and 1-bromo-4-*tert*-butylbenzene (87 μL, 0.50 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and (*S*)-SIPHOS-PE (6.3 mg, 0.0125 mmol), sodium *tert*-butoxide (48.0 mg, 0.50 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.0 mL of xylenes. This procedure afforded the title compound (60 mg, 58%) as a colorless solid, mp 86–90 °C: $[\alpha]^{23}_D$ –2.4 (*c* 5.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.33–7.25 (m, 3 H), 6.92 (d, *J* = 8.1 Hz, 2 H), 4.39 (d, *J* = 14.9 Hz, 1 H), 4.22 (d, *J* = 14.9 Hz, 1 H), 3.44 (d, *J* = 10.0 Hz, 1 H), 3.20 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.08 (dd, *J* = 8.8, 6.1 Hz, 1 H), 2.98–2.91 (m, 0.06 H), 2.61 (d, *J* = 10.0 Hz, 1 H),



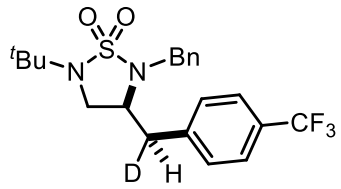
(–)-(1'*R*,3*S*)-2-Benzyl-5-(*tert*-butyl)-3-(-phenylmethyl-d)-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.3, entry 2). The general procedure 2 was employed for the coupling of (*Z*)-1-(3-*d*-allyl)-1-benzyl-3-*tert*-butylsulfamide (71.0 mg, 0.25 mmol) and bromobenzene (53 μL, 0.50 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and (*S*)-SIPHOS-PE (6.3 mg, 0.0125 mmol), sodium *tert*-butoxide (48.0 mg, 0.50 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.0 mL of xylenes. This procedure afforded the title compound (60 mg, 67%) as a colorless solid, mp 108–111 °C: $[\alpha]^{23}_D$ –10.0 (*c* 4.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 7.33–7.19 (m, 4 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 4.39 (d, *J* = 14.9 Hz, 1 H), 4.21 (d, *J* = 14.9 Hz, 1 H), 3.48–3.41 (m, 1 H), 3.16 (dd, *J* = 8.4, 6.7 Hz, 1 H), 3.05

(dd, *J* = 8.7, 6.5 Hz, 1 H), 3.02–2.95 (m, 0.12 H), 2.62 (d, *J* = 10.0 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 136.0, 129.2, 129.0, 128.9, 128.8, 128.1, 127.1, 56.6, 56.4, 50.1, 45.7, 38.4 (t, *J* = 21.0 Hz), 27.6; IR (neat) 2976, 1325, 1153 cm^{-1}; MS (ESI+) 360.1852 (360.1851 calcd for $C_{20}H_{25}DN_2O_2S$, M + Na^+). The diastereoselectivity was determined to be 8:1 by comparing the products obtained from separate reactions of the deuterated and non-deuterated substrates. The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 4% IPA/Hexanes, 0.500 mL/min, λ 210 nm, RT= 18.7 and 20.6 min).



(+)-(1'*R*,3*S*)-3-[(1,1'-Biphenyl)-4-ylmethyl-d]-2-benzyl-5-(*tert*-butyl)-1,2,5-thiadiazolidine 1,1-dioxide (Table 4.3, entry 3). The general procedure 2 was employed for the coupling of (*Z*)-1-(3-*d*-allyl)-1-benzyl-3-*tert*-butylsulfamide (71.0 mg, 0.25 mmol) and 4-bromobiphenyl (117 mg, 0.50 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and (*S*)-SIPHOS-PE (6.3 mg, 0.0125 mmol), sodium *tert*-butoxide (48.0 mg, 0.50 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.0 mL of xylenes. This procedure afforded the title compound (71 mg, 65%) as a yellow solid, mp 116–121 °C: $[\alpha]^{23}_D$ +0.2 (*c* 5.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.51–7.47 (m, 2 H), 7.46–7.40 (m, 4 H), 7.40–7.29 (m, 4 H), 7.09–7.04 (m, 2 H), 4.42 (d, *J* = 14.9 Hz, 1 H), 4.23 (d, *J* = 14.9 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.23 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.12–3.07 (m, 1 H), 3.06–2.99 (m, 0.11 H), 2.67

(d, *J* = 9.8 Hz, 1 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.0, 136.0, 135.6, 129.6, 129.0, 128.8, 128.1, 127.6, 127.5, 127.1, 56.6, 56.4, 50.3, 45.8, 38.0 (t, *J* = 20.0 Hz), 27.6, 1 carbon signal is missing due to incidental equivalence; IR (neat) 2974, 1488, 1320, 1151 cm^{-1}; MS (ESI+) 436.2162 (436.2164 calcd for $C_{26}H_{29}DN_2O_2S$, M + H^+). The diastereoselectivity was determined to be 9:1 by comparing the products obtained from separate reactions of the deuterated and non-deuterated substrates. The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 14.6 and 24.0 min).

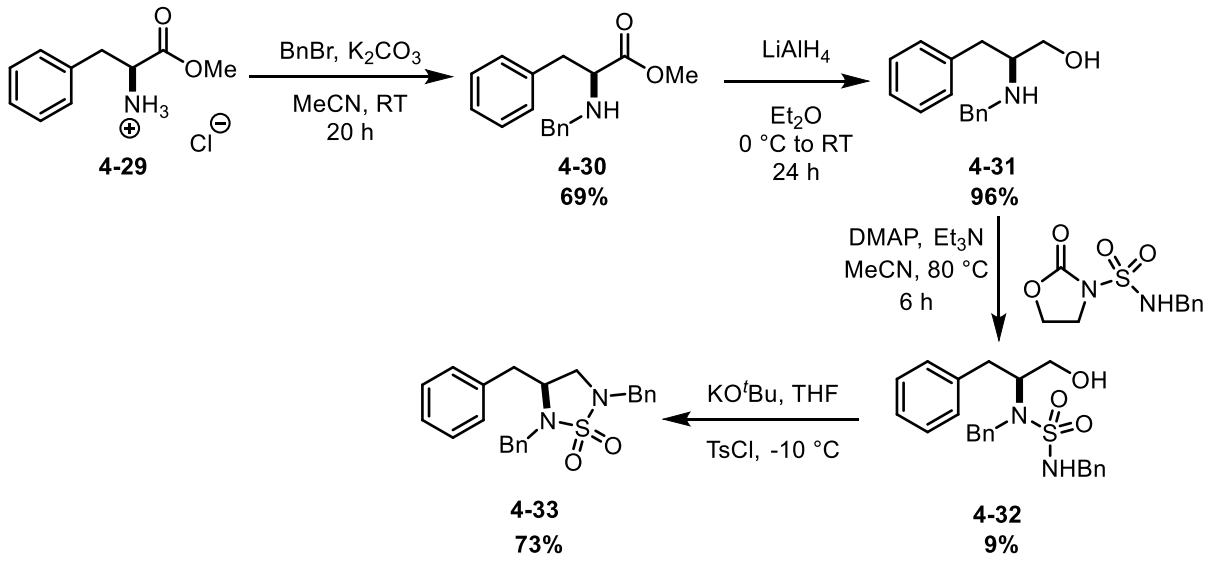


(–)-(1'*R*,3*S*)-2-Benzyl-5-(*tert*-butyl)-3-{[4-(trifluoromethyl)phenyl]methyl-d}-1,2,5-thiadiazolidine-1,1-dioxide (Table 4.3, entry 4). The general procedure 2 was employed for the coupling of (*Z*)-1-(3-*d*-allyl)-1-benzyl-3-*tert*-butylsulfamide (71.0 mg, 0.25 mmol) and 4-bromobenzotrifluoride (70 μL, 0.50 mmol) using a catalyst composed of $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol) and (*S*)-SIPHOS-PE (6.3 mg, 0.0125 mmol), sodium *tert*-butoxide (48.0 mg, 0.50 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 2.0 mL of xylenes. This procedure afforded the title compound (60.0 mg, 56%) as a colorless solid, mp 128–132 °C: $[\alpha]^{23}_D$ –16.6 (*c* 5.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2 H), 7.39–7.28 (m, 4 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 4.39 (d, *J* = 14.7 Hz, 1 H), 4.16 (d, *J* = 14.9 Hz, 1 H), 3.46 (d, *J* = 9.0 Hz, 1 H), 3.23 (dd, *J* = 8.8, 6.6 Hz, 1 H), 3.03 (dd, *J* = 8.9, 5.7 Hz, 1 H), 2.70 (d, *J* = 9.3 Hz, 1 H),

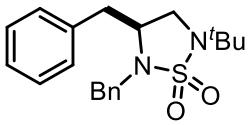
1.40 (s, 9 H); ^{1}H NMR (500 MHz, C_6D_6) δ 7.13–7.21 (m, 4 H), 6.99–7.09 (m, 3 H), 6.57 (d, *J* = 8.1 Hz, 2 H), 4.28 (d, *J* = 14.9 Hz, 1 H), 3.91–3.97(d, *J* = 14.9 Hz, 1 H), 3.02–3.10 (m, 1 H), 2.76 (dd, *J* = 8.8, 6.8 Hz, 1 H), 2.64–2.70 (m, 0.15 H), 2.61 (dd, *J* = 8.8, 5.6 Hz, 1 H), 2.30 (d, *J* = 8.8 Hz, 1 H), 1.24 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 135.7, 129.6, 129.4, 129.0, 128.8, 128.2, 125.8 (q, *J* = 3.90 Hz), 124.2 (q, *J* = 272.8 Hz), 56.5, 56.2, 50.8, 45.8, 38.4 (t, *J* = 19.1 Hz), 27.6; IR (neat) 2972, 1322, 1124 cm^{-1}; MS (ESI+) 428.1723 (428.1724 calcd for $C_{21}H_{24}DF_3N_2O_2S$, M + H^+). The diastereoselectivity was determined to be 7:1 by comparing the products obtained from separate reactions of the deuterated and non-deuterated substrates. The enantiopurity was determined to be 88:12 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 6.0 and 8.3 min). When the reaction was conducted in the presence of water (2 equivalents), the desired product **9d** was obtained with 78% yield 5:1 dr and 89:11 er.

Determination of absolute configuration:

The absolute configuration of the cyclic sulfamide products were assigned by preparing an authentic sample of **4-33** from L-phenylalanine methyl ester hydrochloride as described below. The optical rotation was of the same sign **(–)** as that of the separate authentic sample prepared from L-phenylalanine methyl ester hydrochloride.



Reaction Sequence for Authentic Sample



(–)-(*S*)-2,3-Dibenzyl-5-(*tert*-butyl)-1,2,5-thiadiazolidine 1,1-dioxide (4-33): A 250 mL round bottomed flask equipped with stir bar was flame dried, back filled with nitrogen, and then charged with methyl benzyl-L-phenylalaninate[17] (8.4 mmol, 2.3 g). Anhydrous ether (25 mL) was added, and the reaction mixture was cooled to 0 °C. Lithium aluminum hydride (25 mL of a 1 M solution in ether) was added dropwise then the reaction was warmed to rt and stirred at rt for 24 h. The mixture was then cooled to 0 °C, water (1 mL) was added dropwise followed by sodium hydroxide (1.3 mL of 3 M solution), and additional water (3 mL). The resulting mixture was filtered through celite and concentrated to afford (*S*)-2-(benzylamino)-3-phenylpropan-1-ol as a white solid that was carried onto the next step.

The sulfonylation was performed using a modification of the procedure described

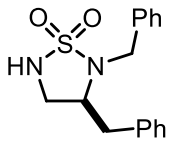
by Wolfe and co-workers.[15] A 100 mL 2-necked round bottom flask equipped with a stir bar, condenser and septum was flame dried and charged with N-(*tert*-butyl)-2-oxooxazolidine-3-sulfonamide (890 mg, 4 mmol) and 4-dimethylaminopyridine (100 mg, 0.8 mmol). Anhydrous acetonitrile (20 mL) and triethylamine (1.7 mL, 12 mmol) were added and the resulting mixture was heated to 80 °C with stirring for 15 min. A solution of (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (1.0 g, 4 mmol) in anhydrous acetonitrile (5 mL) was added dropwise, and the mixture was stirred at 80 °C for 6 h. The mixture was then cooled to rt, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel to afford 130 mg (9%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.8 Hz, 2 H), 7.35–7.15 (m, 6 H), 7.06 (d, J = 6.8 Hz, 2 H), 4.41 (s, 2 H), 4.19–4.10 (m, 1 H), 3.99 (s, 1 H), 3.73–3.65 (m, 1 H), 3.53 (d, J = 4.1 Hz, 1 H), 2.83 (d, J = 6.5 Hz, 1 H), 2.62 (dd, J = 14.0, 8.5 Hz, 1 H), 1.88 (t, J = 5.5 Hz, 1 H), 1.27 (s, 9 H).

A 10 mL flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with the sulfamide prepared above (130.0 mg, 0.35 mmol) and THF (3 mL). The solution was cooled to -10 °C in a brine/ice bath then potassium *tert*-butoxide (80.0 mg, 0.70 mmol) was added in one portion, and the resulting mixture was stirred at –10 °C for 5 min. A solution of tosyl chloride (73.0 mg, 0.39 mmol) THF (1.3 mL) was then added dropwise and the mixture was stirred at –10 °C for 10 min at which time TLC analysis indicated the starting material had been completely consumed. The mixture was warmed to rt, quenched with 5 mL water, and extracted with ether (2 x 5 mL). The organic layers were combined, filtered through a plug of celite, and the solvent was removed under reduced pressure. The crude product

was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant. This procedure afforded the title compound (91.0 mg, 73 %) as a colorless solid. $[\alpha]^{23}_{D}$ –10.7 (*c* 8.4, $CHCl_3$); The spectroscopic properties of this compound were identical to the compound synthesized via the Pd-catalyzed carboamination reaction. The enantiopurity was determined to be >99:1 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 4.0% IPA/Hexanes, 0.5 mL/min, λ 210 nm, RT= 18.4 and 20.7 min).

Deprotection Methods:

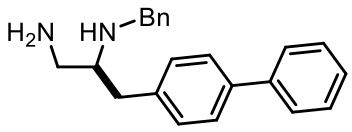
Cleavage of *N-tert*-butyl group



(–)-(*S*)-2,3-Dibenzyl-1,2,5-thiadiazolidine-1,1-dioxide (4-25). A round bottom flask equipped with a stirbar and a septum was charged with **4-24** (55.2 mg, 0.15 mmol), hexanes (1.0 mL) and trifluoroacetic acid (0.75 mL). The resulting mixture was stirred at rt for 24 h, and then the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel to afford the title compound (44.0 mg, 98%) as a colorless solid, mp 69–73 °C: $[\alpha]^{23}_{D}$ –9.1 (*c* 3.9, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.21 (m, 8 H), 7.07–7.02 (m, 2 H), 4.35–4.25 (m, 2 H), 4.22 (t, *J* = 7.5 Hz, 1 H), 3.62 (ddt, *J* = 8.8, 6.7, 4.6 Hz, 1 H), 3.35 (ddd, *J* = 11.9, 7.9, 6.6 Hz, 1 H), 3.19 (ddd, *J* = 11.7, 7.2, 4.3 Hz, 1 H), 2.87 (dd, *J* = 13.6, 5.0 Hz, 1 H), 2.62 (dd, *J* = 13.6, 8.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 135.7, 129.4, 129.1, 129.0, 128.9, 128.4, 127.3, 61.6, 49.8, 45.1, 39.3; IR (neat) 3302, 2921, 1287, 1145 cm^{-1}; MS

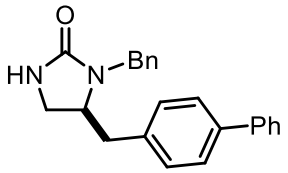
(ESI+) 303.1161 (303.1162 calcd for $C_{16}H_{18}N_2O_2S$, M + H^+). The enantiopurity was determined to be 6:94 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 0.5 mL/min, λ 210 nm, RT= 51.5 and 54.9 min).

Cleavage of *N-tert*-butyl group and sulfonyl group



(+)-(*S*)-3-([1,1'-Biphenyl]-4-yl)-*N*^{2}-benzylpropane-1,2-diamine (4-27). A 10 mL round bottom flask equipped with a reflux condenser and a stir bar was charged with (*S*)-3-([1,1'-biphenyl]-4-ylmethyl)-2-benzyl-5-(*tert*-butyl)-1,2,5-thiadiazolidine-1,1-dioxide (74.1 mg, 0.17 mmol) and phenol (50.0 mg, 0.53 mmol). Aqueous 2 M hydrobromic acid (2 mL, 4 mmol) was added, the reaction mixture was heated at 130 °C for 24 h, then was cooled to rt. The mixture was diluted with water (5 mL) and ether (5 mL) then solid sodium hydroxide (~2.3 g) was added until the mixture reached pH ≥ 10. The layers were separated, and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were dried with sodium sulfate, and then passed through a plug of celite. The solvent was removed under reduced pressure to afford the title compound (46 mg, 85%) as a yellow oil: $[\alpha]^{23}_D$ +1.6 (*c* 4.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.55 (m, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.36–7.19 (m, 8 H), 3.86–3.77 (m, 2 H), 2.90–2.79 (m, 3 H), 2.78–2.69 (m, 1 H), 2.63–2.54 (m, 1 H), 1.53–1.38 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 140.8, 139.3, 138.4, 129.8, 128.9, 128.5, 128.2, 127.3, 127.3, 127.1, 127.0, 60.5, 51.5, 44.6, 38.7; IR (neat) 3292, 3025, 1486, 1451, 696 cm^{-1}; MS (ESI+) 317.2015 (317.2012 calcd for $C_{22}H_{24}N_2$,

M + H^+). The enantiopurity was determined by further elaborating diamine **7** to urea **S2** by reaction with CDI as outlined below.



(+)-(*S*)-5-([1,1'-Biphenyl]-4-ylmethyl)-1-benzylimidazolidin-2-one (4-28). A flame-dried round bottom flask equipped with a stirbar and reflux condenser was charged with **4-27** (46 mg, 0.15 mmol) and THF (1 mL). A solution of 1,1'-carbonyldiimidazole (35 mg, 0.22 mmol) THF (1 mL) was added the resulting mixture was heated to reflux with stirring for 24 h. The mixture was then cooled to rt and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using dichloromethane/methanol as eluant to afford the title compound (46 mg, 89%) as a colorless solid, mp 110–114 °C: $[\alpha]^{23}_D$ +29.4 (*c* 3.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.51 (m, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 7.45–7.39 (m, 2 H), 7.37–7.25 (m, 6 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 4.99 (s, br, 1 H), 4.87 (d, *J* = 15.3 Hz, 1 H), 4.09 (d, *J* = 15.5 Hz, 1 H), 3.74 (tdd, *J* = 8.8, 6.9, 4.5 Hz, 1 H), 3.28 (t, *J* = 8.6 Hz, 1 H), 3.18–3.05 (m, 2 H), 2.65 (dd, *J* = 13.5, 9.2 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 140.8, 139.9, 137.3, 135.9, 129.7, 128.9, 128.8, 128.3, 127.7, 127.5, 127.5, 127.1, 56.0, 45.5, 43.8, 38.4; IR (neat) 3215, 1690, 1486, 1487, 1449 cm^{-1}; MS (ESI+) 343.1804 (343.1805 calcd for $C_{23}H_{22}N_2O$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.0 mL/min, λ 254 nm, RT= 26.7 and 49.0 min).

Asymmetric Synthesis of 6-Membered Cyclic Sulfamides

Synthesis of Substrates:

General procedure 3 for the synthesis of secondary amines:

Secondary amines were prepared from the corresponding ketones by a two-step procedure involving imine formation followed by Grignard addition to the imine.

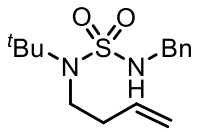
Symmetrical ketone (1 equiv.), primary amine (1 equiv.), 4 Å molecular sieves (200 mg/mmol), and dichloromethane (2 M) were added to a flame-dried flask equipped with stir bar. The mixture was vigorously stirred until complete consumption of the starting materials as determined by TLC. Then, the mixture was filtered through celite and the solvent was removed under reduced pressure.

A flame-dried round bottom flask was equipped with stir bar and then charged with allylmagnesium bromide (1M in ether). This solution was cooled to 0 °C and then a solution of imine (0.4 M in THF) was added dropwise. The reaction was allowed to come to rt, and then stirred overnight. Then, the flask was cooled to 0 °C in an ice bath and slowly quenched with saturated aqueous ammonium chloride (0.5 mL/mmol). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 10 mL/mmol). The organic layers were combined and washed with brine (10 mL/ mmol), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was

purified by flash chromatography on silica gel.

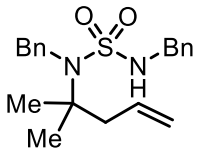
General procedure 4 for the synthesis of substrates:

A flame dried two neck round bottom flask equipped with stir bar, condenser, and septum was cooled under a stream of nitrogen. This flask was charged with DMAP (0.20 equiv.) and oxazolidin-2-one substrate (1.0 equiv.). Anhydrous acetonitrile (5 mL/mmol) was added followed by triethylamine (3.0 equiv.). This mixture was heated at 80 °C for 15 minutes, and then the allyl amine was added dropwise. This was allowed to stir for 16-18 h. The reaction mixture was brought to room temperature, and then the solvent was removed under reduced pressure. The material was redissolved in ethyl acetate (2.5 mL/mmol) and washed 2x 1 M HCl (2.5 mL/mmol), and 1x brine (2.5 mL/mmol). The organic layer was dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography using hexanes/ethyl acetate as eluant.



***N'*-benzyl-*N*-(*tert*-butyl)-*N*-(but-3-en-1-yl)sulfamide (4-34).** The general procedure 4 was employed for the sulfonylation of *N*-(*tert*-butyl)but-3-en-1-amine (1.34 g, 10.5 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.43 g, 9.5 mmol). This procedure afforded the title compound (670 mg, 24%) as a colorless solid, mp 44–47 °C: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38–7.33 (m, 4 H), 7.33–7.29 (m, 1 H), 5.80–5.73 (m, 1 H), 5.09 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.04 (d, *J* = 10.2 Hz, 1 H), 4.21 (t, *J* = 6.1 Hz, 2 H), 4.16 (d, *J* = 6.1 Hz, 2 H), 3.34–3.30 (m, 2 H), 2.46–2.41 (m, 2 H), 1.46 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ

136.8, 135.2, 129.0, 128.3, 128.1, 116.9, 58.9, 47.6, 46.6, 36.8, 29.6; IR (neat) 3322, 1317, 1135, 1088 cm^{-1}. MS (ESI+) 297.1629 (297.1631 calcd for $C_{15}H_{24}N_2O_2S$, M + H^+).



***N*-Benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (4-36).**

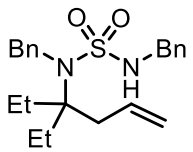
General procedure 3 was used to generate *N*-benzyl-2-methylpent-4-en-2-amine. Acetone (4.4 mL, 60 mmol) and benzylamine (6.6 ml, 60 mmol) were stirred in the presence of 4 Å molecular sieves (12 g) and dichloromethane (30 mL) for 4 h. The solution was filtered through celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylpropan-2-imine which was used without further purification.

The Grignard reaction was performed according to general procedure 3 by adding crude *N*-benzylpropan-2-imine in 150 mL THF to allylmagnesium bromide (150 mmol, 1M solution in ether). Workup and subsequent purification by column chromatography afforded *N*-benzyl-2-methylpent-4-en-2-amine as a yellow oil (9.9 g, 87% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 4H), 7.25–7.21 (m, 1H), 5.93–5.82 (m, 1H), 5.15–5.08 (m, 2H), 3.72 (s, 2H), 2.25 (d, *J* = 7.4 Hz, 2H), 1.15 (s, 6H).

General procedure 4 was used to sulfonylate *N*-benzyl-2-methylpent-4-en-2-amine (4.3 g, 22.5 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (5.2 g, 20.4 mmol) to afford the title compound (3.0 g, 41%) as a colorless solid, mp 75–77 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.36–7.20 (m, 8H), 5.92–5.80 (m, 1H), 5.12 (s, 1H), 5.09 (s, 1H), 4.58 (s, 2H), 4.17 (t, *J* = 5.5 Hz, 1H), 4.13 (d, *J* = 5.4 Hz, 2H), 2.64 (d, *J* =

7.3 Hz, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.08, 136.88, 134.50, 128.90, 128.64, 128.23, 128.07, 127.22, 118.74, 62.58, 50.79, 47.73, 45.95, 27.88; IR (neat) 3330, 1453, 1320, 1132 cm^{-1}; MS (ESI+) 359.1791 (359.1788 calcd for $C_{20}H_{26}N_2O_2S$, M + H+).

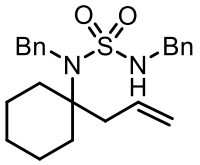


***N*-Benzyl-*N'*-benzyl-*N*-(3-ethylhex-5-en-3-yl)sulfamide.** General procedure 3 was used to generate *N*-benzyl-3-ethylhex-5-en-3-amine. 3-Pentanone (3.2 mL, 30 mmol) and benzylamine (3.3 ml, 30 mmol) were stirred in the presence of 4 Å molecular sieves (6 g) and dichloromethane (15 mL) for 24 h. The solution was filtered through celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylpentan-3-imine which was used without further purification.

The Grignard reaction was performed according to general procedure 3 by adding crude *N*-benzylpentan-3-imine in 75 mL THF to allylmagnesium bromide (75 mmol, 1M solution in ether). Workup and subsequent purification by column chromatography afforded *N*-benzyl-3-ethylhex-5-en-3-amine as a yellow oil (2.6 g, 40% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.9 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.25–7.21 (m, 1H), 5.89–5.79 (m, 1H), 5.17–5.05 (m, 2H), 3.61 (s, 2H), 2.17 (dt, *J* = 7.4, 1.3 Hz, 2H), 1.42 (qd, *J* = 7.4, 2.2 Hz, 4H), 0.86 (t, *J* = 7.4 Hz, 6H).

General procedure 4 was used to sulfonylate *N*-benzyl-3-ethylhex-5-en-3-amine (2.64 g, 12.2 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.83 g, 11 mmol) to afford the title compound (450 mg, 11%) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2 H), 7.34–7.31 (m, 2 H), 7.30–7.24 (m, 4 H), 7.18–7.15 (m, 2 H), 5.90 (ddt, *J* =

17.1, 10.2, 7.2 Hz, 1 H), 5.14–5.12 (m, 1 H), 5.12–5.10 (m, 1 H), 4.59 (s, 2 H), 4.14 (d, *J* = 6.1 Hz, 2 H), 4.08 (t, *J* = 6.1 Hz, 1 H), 2.64 (d, *J* = 7.3 Hz, 2 H), 1.89–1.78 (m, 4 H), 0.94 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 140.3, 137.1, 134.5, 128.8, 128.6, 128.2, 128.0, 127.6, 127.2, 118.5, 69.9, 50.8, 48.0, 39.7, 28.4, 8.9; IR (neat) 3296, 1318, 1144 cm^{-1}; MS (ESI+) 387.2106 (387.2101 calcd for $C_{22}H_{30}N_2O_2S$, M + H+).



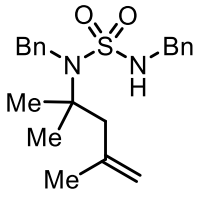
***N*-Benzyl-*N'*-benzyl-*N*-(1-allylcyclohexyl)sulfamide.** General procedure 3 was used to generate 1-allyl-*N*-benzylcyclohexan-1-amine. Cyclohexanone (2.1 mL, 20 mmol) and benzylamine (2.2 ml, 20 mmol) were stirred in the presence of 4 Å molecular sieves (4 g) and dichloromethane (10 mL) for 4 h. The solution was filtered through celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylcyclohexanimine which was used without further purification.

The Grignard reaction was performed according to general procedure 3 by adding crude *N*-benzylcyclohexanimine in 50 mL THF to allylmagnesium bromide (50 mmol, 1M solution in ether). Workup and subsequent purification by column chromatography afforded 1-allyl-*N*-benzylcyclohexan-1-amine as a yellow oil (3.1 g, 68% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.9 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.25–7.21 (m, 1H), 5.14–5.07 (m, 2H), 3.65 (s, 2H), 2.26 (d, *J* = 7.4 Hz, 2H), 1.72–1.30 (m, 10H).

General procedure 4 was used to sulfonylate 1-allyl-*N*-benzylcyclohexan-1-amine (3.1 g, 13.9 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (3.2 g, 12.5 mmol) to afford the

title compound (1.23 g, 25%) as a colorless solid, mp 77–79 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.35–7.22 (m, 6H), 7.18–7.15 (m, 2H), 6.03–5.93 (m, 1H), 5.19–5.11 (m, 1H), 4.59 (s, 2H), 4.11 (d, *J* = 5.7 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 1H), 2.79 (d, *J* = 7.2 Hz, 2H), 2.19 (d, *J* = 12.8 Hz, 2H), 1.81 (td, *J* = 12.7, 3.7 Hz, 2H), 1.67–1.53 (m, 3H), 1.48–1.35 (m, 2H), 1.27–1.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 137.0, 134.6, 128.8, 128.6, 128.2, 128.0, 127.3, 127.2, 118.5, 66.4, 50.2, 47.8, 38.4, 35.3, 25.3, 23.1; IR (neat) 3333, 1455, 1414, 1333, 1148 cm^{-1}; MS (ESI+) 399.2103 (399.2101 calcd for $C_{23}H_{30}N_2O_2S$, M + H+).



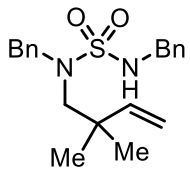
***N*-Benzyl-*N'*-benzyl-*N*-(2,4-dimethylpent-4-en-2-yl)sulfamide (4-45).** General procedure 3 was used to generate *N*-benzyl-2,4-dimethylpent-4-en-2-amine. Acetone (4.4 mL, 60 mmol) and benzylamine (6.6 mL, 60 mmol) were stirred in the presence of 4 Å molecular sieves (12 g) and dichloromethane (30 mL) for 4 h. The solution was filtered through celite, and the solvent was removed under reduced pressure to afford crude *N*-benzylpropan-2-imine which was used without further purification.

The Grignard reaction was performed according to general procedure 3 by adding crude *N*-benzylpropan-2-imine in 150 mL THF to allylmagnesium chloride (150 mmol, 1M solution in ether). Workup and subsequent purification by column chromatography afforded *N*-benzyl-2,4-dimethylpent-4-en-2-amine as a yellow oil (3.05 g, 25% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.7 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J*

= 7.1 Hz, 1H), 4.91 (s, 1H), 4.73 (s, 1H), 3.76 (s, 2H), 2.24 (s, 2H), 1.85 (s, 3H), 1.18 (s, 6H).

General procedure 4 was used to sulfonylate *N*-benzyl-2,4-dimethylpent-4-en-2-amine (2.4 g, 12 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (2.56 g, 10.0 mmol) to afford the title compound (1.4 g, 37%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.35–7.21 (m, 8H), 4.93–4.91 (m, 1H), 4.79 (s, 1H), 4.60 (s, 2H), 4.23 (t, *J* = 6.1 Hz, 1H), 4.12 (d, *J* = 6.1 Hz, 2H), 2.64 (s, 2H), 1.81 (s, 3H), 1.50 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 140.1, 137.0, 128.9, 128.6, 128.2, 128.0, 127.3, 127.2, 116.2, 63.3, 50.8, 48.3, 47.7, 28.3, 25.3; IR (neat) 3300, 1317, 1134 cm^{-1}; MS (ESI+) 373.1948 (373.1944 calcd for $C_{21}H_{28}N_2O_2S$, M + H+).



***N*-benzyl-*N'*-benzyl-*N*-(2,2-dimethylbut-3-en-1-yl)sulfonamide (4-43).** 2,2-Dimethylbut-3-enoic acid[18] (1.1 g, 10 mmol) was suspended in dichloromethane (30 mL) and trimethylamine was added (2.8 mL, 20 mmol). The mixture was cooled to 0 °C, and then ethyl chloroformate (0.96 mL, 10 mmol) was added dropwise. The solution was stirred 30 minutes, and then benzylamine was added dropwise (1.3 mL, 12 mmol). The reaction was allowed to come to rt, and then stirred overnight. The reaction was quenched with saturated sodium bicarbonate (3 mL/mmol). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 30 mL/mmol). The organic layers were combined and washed with brine (10 mL/ mmol), dried with anhydrous sodium sulfate, filtered, and

concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford *N*-benzyl-2,2-dimethylbut-3-enamide as a yellow oil (1.3 g, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.30–7.27 (m, 1H), 7.25–7.21 (m, 3H), 6.02 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.23 (d, *J* = 17.5 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 4.41 (d, *J* = 5.7 Hz, 2 H), 1.33 (s, 6H).

N-benzyl-2,2-dimethylbut-3-enamide was added to a flame dried three-necked round bottom flask equipped with reflux condenser. Anhydrous diethyl ether (13 mL) was added, and then the solution was brought to 0 °C. Lithium aluminum hydride (20 mL of a 1 M solution in diethyl ether, 20 mmol) was added dropwise, and then the mixture was refluxed overnight. The crude product was purified by flash chromatography on silica gel to afford *N*-benzyl-2,2-dimethylbut-3-en-1-amine as a yellow oil (1.0 g, 82%).

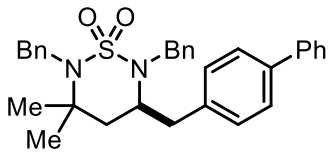
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 4H), 7.26–7.21 (m, 1H), 5.78 (dd, *J* = 17.2, 11.1 Hz, 1H), 5.02–4.95 (m, 2H), 3.79 (s, 2H), 2.43 (s, 2H), 1.03 (s, 6H).

General procedure 4 was used to sulfonylate *N*-benzyl-2,2-dimethylbut-3-en-1-amine (1.0 g, 5.3 mmol) with 3-(benzylsulfonyl)oxazolidin-2-one (1.24 g, 4.85 mmol) to afford the title compound (1.61 g, 93%) as a colorless solid, mp 69–71 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.37–7.27 (m, 6H), 7.22–7.18 (m, 2H), 5.93 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 5.02 (d, *J* = 10.6 Hz, 1H), 4.50 (s, 2H), 4.10 (d, *J* = 6.0 Hz, 2H), 4.07–4.01 (t, *J* = 6.1 Hz, 1H), 3.21 (s, 2H), 1.09 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 136.9, 136.6, 128.9, 128.9, 128.8, 128.1, 128.1, 112.4, 58.2, 53.5, 47.7, 39.5, 25.5, one peak is missing due to incidental equivalence; IR (neat) 3310, 2965, 1320, 1131 cm^{-1}; MS (ESI+) 359.1788 (359.1788 calcd for $C_{20}H_{26}N_2O_2S$, M

+ H+).

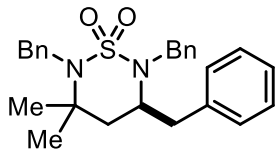
General procedure 5 for asymmetric Pd-catalyzed carboamination reactions.

An oven-dried test tube tube equipped with a stir bar and septum was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol %), (*S*)-SIPHOS-PE (5 mol %), the sulfamide substrate (1.0 equiv), and NaO^{t}Bu (2.0 equiv). The flask was purged with N_2, and then the aryl or alkenyl halide (1.40–2.0 equiv), water (0 or 2.0 equiv.), and xylenes (0.125 M) were added. The resulting mixture was heated to 120 °C with stirring for 18 h. The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6 mL/mmol substrate) was added. The mixture was extracted with ethyl acetate (3 x 2 mL) and then the combined organic layers were dried over anhydrous Na_2SO_4, filtered through a celite plug, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as eluant.



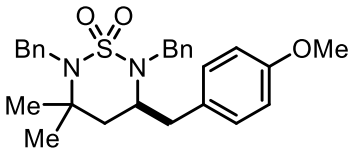
(S)-5-([1,1'-biphenyl]-4-ylmethyl)-2,6-dibenzyl-3,3-dimethyl-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 1). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and 4-bromobiphenyl (104 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (80 mg, 78%) as a white solid, mp

174–178 °C: $[\alpha]^{23}_D$ -154.5 (*c* 1.98, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 6H), 7.36–7.29 (m, J = 7.7 Hz, 5H), 7.27–7.22 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.72 (d, *J* = 15.8 Hz, 1H), 4.64 (d, *J* = 16.8 Hz, 1H), 4.41–4.49 (m, 1H), 4.32 (d, *J* = 15.8 Hz, 1H), 4.15 (d, *J* = 16.8 Hz, 1H), 2.92 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.64 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.07 (t, *J* = 10 Hz, 1H), 1.46 (dd, *J* = 14.3, 2.6 Hz, 1H), 1.32 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 140.4, 139.7, 138.3, 136.4, 129.6, 129.0, 128.6, 128.6, 128.1, 127.5, 127.5, 127.4, 127.2, 127.1, 60.5, 57.2, 50.1, 45.8, 40.46, 38.87, 31.0, 23.0, 1 carbon signal is missing due to incidental equivalence; IR (neat) 1488, 1452, 1332, 1153, 1137 cm^{-1}. MS (ESI+) 511.2413 (511.2414 calcd for $C_{32}H_{34}N_2O_2S$, M + H^+). The enantiopurity was determined to be 97:3 er by chiral HPLC analysis when 4-bromobiphenyl served as electrophile (Chiralcel ODH, 15 cm x 4.6 mm, 7% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 16.5 and 29.7 min). When 4-iodobiphenyl was used as the electrophile, the enantioselectivity was less reproducible providing enantiomeric ratios that ranged from 82:18 er to 91.5:8.5 er.



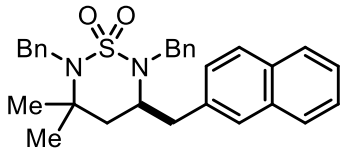
(S)-2,5,6-tribenzyl-3,3-dimethyl-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 4). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and bromobenzene (42 µL, 0.4 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.60 mmol), a reaction

temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (80 mg, 92%) as a colorless solid, mp 149–153 °C: $[\alpha]^{23}_{D}$ -65 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.9 Hz, 5H), 7.32 (td, *J* = 7.5, 2.6 Hz, 6H), 7.28–7.21 (m, 4H), 7.21–7.17 (m, 1H), 7.06 (d, *J* = 7.0 Hz, 2H), 4.71 (d, *J* = 15.8 Hz, 1H), 4.64 (d, *J* = 16.8 Hz, 1H), 4.41 (dddd, *J* = 12.7, 10.1, 4.8, 2.9 Hz, 1H), 4.30 (d, *J* = 15.8 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H), 2.89 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.58 (dd, *J* = 13.6, 10.2 Hz, 1H), 2.03 (dd, *J* = 14.3, 12.2 Hz, 1H), 1.39 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.28 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 138.4, 137.4, 129.2, 128.8, 128.6, 128.5, 128.1, 127.5, 127.4, 127.2, 126.9, 60.4, 57.3, 50.1, 45.8, 40.9, 38.7, 31.0, 22.9.; IR (neat) 1495, 1452, 1330, 1151, 1136 cm^{-1}. MS (ESI+) 435.2106 (435.2101 calcd for $C_{26}H_{30}N_2O_2S$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 3% IPA/Hexanes, 0.8 mL/min, λ 210 nm, RT= 16.7 and 22.3 min).



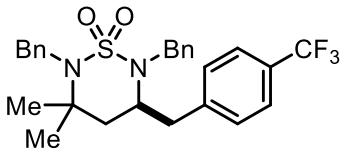
(S)-2,6-dibenzyl-5-(4-methoxybenzyl)-3,3-dimethyl-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 3). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and 4-bromoanisole (50 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (55 mg, 59%) as a colorless solid, mp 135–138 °C: $[\alpha]^{23}_{D}$ -78 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6

Hz, 4H), 7.32 (td, J = 7.5, 1.4 Hz, 4H), 7.27–7.21 (m, 2H), 6.97 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 4.70 (d, J = 15.9 Hz, 1H), 4.63 (d, J = 16.8 Hz, 1H), 4.35 (dddd, J = 12.5, 10.1, 4.8, 2.8 Hz, 1H), 4.28 (d, J = 15.8 Hz, 1H), 4.13 (d, J = 16.8 Hz, 1H), 3.77 (s, 3H), 2.82 (dd, J = 13.7, 4.8 Hz, 1H), 2.52 (dd, J = 13.7, 10.2 Hz, 1H), 2.00 (dd, J = 14.3, 12.3 Hz, 1H), 1.39 (dd, J = 14.3, 2.8 Hz, 1H), 1.28 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 140.4, 138.4, 130.1, 129.3, 128.6, 128.5, 128.1, 127.5, 127.4, 127.2, 114.2, 60.4, 57.5, 55.4, 50.0, 45.7, 40.0, 38.7, 31.0, 22.8.; IR (neat) 1604, 1512, 1494, 1454, 1329, 1152, 1136 cm^{-1}. MS (ESI+) 465.2204 (465.2206 calcd for $C_{27}H_{32}N_2O_3S$, M + H^+). The enantiopurity was determined to be 98:2 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 4% IPA/Hexanes, 1.00 mL/min, λ 205 nm, RT= 32.9 and 38.9 min).



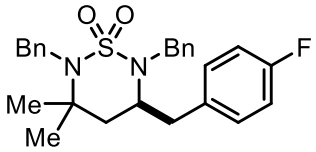
(S)-2,6-dibenzyl-3,3-dimethyl-5-(naphthalen-2-ylmethyl)-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 2). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and 2-bromonapthalene (83 mg, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (72 mg, 74%) as a colorless solid, 168–172 °C: $[\alpha]^{23}_D$ -43 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.77 (m, 1H), 7.75–7.70 (m, 2H), 7.48–7.41 (m, 7H), 7.35–7.28 (m, 4H), 7.25–7.19 (m, 2H), 4.75 (d, *J*

= 15.8 Hz, 1H), 4.64 (d, *J* = 16.8 Hz, 1H), 4.51 (dddd, *J* = 12.6, 10.0, 4.8, 2.8 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H), 3.05 (dd, J = 13.5, 4.8 Hz, 1H), 2.73 (dd, *J* = 13.6, 10.2 Hz, 1H), 2.08 (dd, *J* = 14.3, 12.2 Hz, 1H), 1.41 (dd, *J* = 14.4, 2.9 Hz, 1H), 1.26 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 138.4, 134.9, 133.6, 132.5, 128.6, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.2, 127.2, 126.3, 125.8, 60.5, 57.4, 50.2, 45.8, 41.1, 38.8, 31.0, 22.9; IR (neat) 1495, 1452, 1331, 1151, 1136 cm^{-1}. MS (ESI+) 485.2260 (485.2257 calcd for $C_{30}H_{32}N_2O_2S$, M + H^+). The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 4% IPA/Hexanes, 1.0 mL/min, λ 254 nm, RT= 30.4 and 33.5 min).



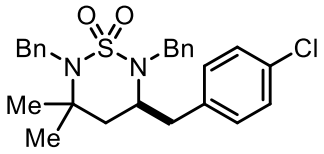
(S)-2,6-dibenzyl-3,3-dimethyl-5-(4-(trifluoromethyl)benzyl)-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 5). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and 4-bromobenzotrifluoride (56 μL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.001 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (74 mg, 73%) as a colorless solid, mp 159–161 °C: $[\alpha]^{23}_D$ -77 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 11.0, 7.8 Hz, 4H), 7.36–7.20 (m, 8H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.64 (t, *J* = 16.3 Hz, 2H), 4.42 (dddd, *J* = 12.0, 9.1, 6.1, 3.1 Hz, 1H), 4.31 (d, *J* = 15.8 Hz, 1H), 4.18 (d, *J* = 16.8 Hz, 1H), 2.92 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.68 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.09 (dd, *J*

= 14.3, 11.9 Hz, 1H), 1.41 (dd, *J* = 14.3, 3.1 Hz, 1H), 1.32 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 141.4, 140.2, 137.8, 129.4, 129.1 (q, J_{CF} = 31.7 Hz), 128.6, 128.6, 128.1, 127.6, 127.4, 127.2, 125.6 (q, J_{CF} = 3.5 Hz), 124.3 (q, J_{CF} = 272.8 Hz), 60.4, 56.9, 50.4, 45.8, 40.5, 39.0, 30.7, 23.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ –62.54; IR (neat) 1495, 1452, 1328, 1154, 1136 cm^{-1}. MS (ESI+) 503.1977 (503.1975 calcd for $C_{27}H_{29}F_3N_2O_2S$, M + H^+). The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 4% IPA/Hexanes, 0.50 mL/min, λ 210 nm, RT= 15.6 and 17.9 min).



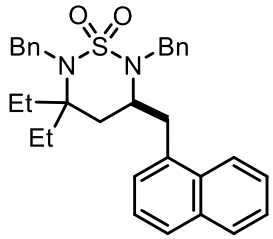
(S)-2,6-dibenzyl-5-(4-fluorobenzyl)-3,3-dimethyl-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 6). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and 1-bromo-4-fluorobenzene (44 μL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.001 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (82 mg, 91%) as a colorless solid, mp 132–133 °C: $[\alpha]^{23}_D$ -68 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 7.1 Hz, 2H), 7.28–7.35 (m, 4H), 7.27–7.22 (m, 2H), 7.02–6.96 (m, 2H), 6.91 (t, *J* = 8.6 Hz, 2H), 4.69 (d, *J* = 15.8 Hz, 1H), 4.63 (d, *J* = 16.8 Hz, 1H), 4.36 (dddd, *J* = 12.3, 8.8, 5.3, 2.9 Hz, 1H), 4.28 (d, *J* = 15.8 Hz, 1H), 4.15 (d, *J* = 16.8 Hz, 1H), 2.84 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.56 (dd, *J* = 13.9, 9.6 Hz, 1H), 2.04 (dd, *J* = 14.3, 12.1 Hz, 1H), 1.39 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.30 (s, 3H), 1.14 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 161.8 (d, 243.8 Hz), 140.30, 138.16, 133.0 (d, J_{CF} = 3.8 Hz), 130.5 (d, J_{CF} = 7.5 Hz), 128.60, 128.55, 128.1, 127.6, 127.4, 127.2, 115.56 (d, J_{CF} = 21.2 Hz), 60.4, 57.3, 50.2, 45.8, 39.9, 38.8, 30.9, 23.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ –116.35– –116.21 (m); IR (neat) 1495, 1452, 1330, 1153, 1137 cm^{-1}. MS (ESI+) 453.2007 (453.2007 calcd for $C_{26}H_{29}FN_2O_2S$, M + H^+). The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 4% IPA/Hexanes, 0.50 mL/min, λ 210 nm, RT= 16.1 and 17.7 min).



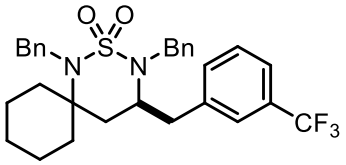
2,6-dibenzyl-5-(4-chlorobenzyl)-3,3-dimethyl-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 8). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(2-methylpent-4-en-2-yl)sulfamide (72.0 mg, 0.20 mmol) and 1-bromo-4-chlorobenzene (77 mg, 0.4 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.60 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (72 mg, 77%) as a colorless solid, mp 145–148 °C: $[\alpha]^{23}_D$ -80 (*c* 1.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2H), 7.38 (d, J = 7.0 Hz, 2H), 7.31 (ddd, J = 9.8, 8.4, 6.7 Hz, 4H), 7.27–7.22 (m, 2H), 7.20–7.16 (m, 2H), 6.98–6.94 (m, 2H), 4.69 (d, J = 15.8 Hz, 1H), 4.63 (d, J = 16.8 Hz, 1H), 4.36 (dddd, *J* = 12.3, 8.8, 5.4, 2.9 Hz, 1H), 4.28 (d, *J* = 15.8 Hz, 1H), 4.15 (d, *J* = 16.8 Hz, 1H), 2.84 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.56 (dd, *J* = 13.9, 9.5 Hz, 1H), 2.04 (dd, *J* = 14.3, 12.1 Hz, 1H), 1.38 (dd, *J* = 14.3, 3.0 Hz, 1H), 1.30 (s, 3H), 1.14 (s, 3H), contains 5-10% of an inseparable impurity; ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 138.1, 135.8,

132.6, 130.4, 128.9, 128.6, 128.6, 128.0, 127.6, 127.4, 127.2, 60.4, 57.1, 50.2, 45.7, 40.1, 38.7, 30.9, 23.1.; IR (neat) 1493, 1452, 1320, 1136 cm^{-1}. MS (ESI+) 469.1710 (469.1711 calcd for $C_{26}H_{29}ClN_2O_2S$, M + H^+). The enantiopurity was determined to be 97:3 er by chiral HPLC analysis (Chiralcel ADH, 15 cm x 4.6 mm, 4% IPA/Hexanes, 1.0 mL/min, λ 210 nm, RT= 26.2 and 28.6 min).



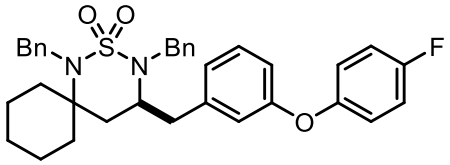
(S)-2,6-dibenzyl-3,3-diethyl-5-(naphthalen-1-ylmethyl)-1,2,6-thiadiazinane 1,1-dioxide (Table 4.4, entry 9). The general procedure 5 was employed for the coupling of *N*-benzyl-*N'*-benzyl-*N*-(3-ethylhex-5-en-3-yl)sulfamide (77.0 mg, 0.20 mmol) and 1-bromonapthalene (56 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (89 mg, 86%) as a colorless solid, mp 58–62 °C: $[\alpha]^{23}_D$ -59 (*c* 2.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.78 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.61–7.57 (m, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.48–7.40 (m, 4H), 7.40–7.35 (m, 2H), 7.34–7.28 (m, 3H), 7.27–7.22 (m, 2H), 4.59 (d, *J* = 15.1 Hz, 1H), 4.51 (d, *J* = 15.1 Hz, 1H), 4.47 (d, *J* = 16.6 Hz, 1H), 4.36 (d, *J* = 16.6 Hz, 1H), 4.15 (ddt, *J* = 14.4, 9.4, 4.3 Hz, 1H), 3.34 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.08 (dd, *J* = 13.7, 10.0 Hz, 1H), 2.35 (dd, *J* = 14.9, 12.1 Hz, 1H), 1.67 (dq, *J* = 15.1, 7.6 Hz, 1H), 1.60–1.37 (m, 3H), 1.31 (dd, *J* = 15.0, 4.1 Hz, 1H), 0.70 (t, J = 7.3 Hz, 3H), 0.35 (t, J = 7.5 Hz, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 140.1, 137.8, 134.0, 133.7, 131.9, 129.0, 128.8, 128.8, 128.5, 128.1, 127.9, 127.6, 127.6, 127.2, 126.3, 125.8, 125.5, 123.6, 66.0, 56.3, 52.8, 46.2, 39.2, 30.5, 29.4, 29.0, 9.2, 7.9.; IR (neat) 1495, 1454, 1331, 1153 cm^{-1}. MS (ESI+) 513.2572 (513.2570 calcd for $C_{32}H_{36}N_2O_2S$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ODH, 15 cm x 4.6 mm, 2% IPA/Hexanes, 0.75 mL/min, λ 210 nm, RT= 17.1 and 20.2min).



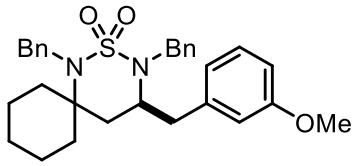
(S)-1,3-dibenzyl-4-(3-(trifluoromethyl)benzyl)-2-thia-1,3-diazaspiro[5.5]undecane 2,2-dioxide (Table 4.4, entry 11). The general procedure 5 was employed for the coupling of *N*-Benzyl-*N'*-benzyl-*N*-(1-allylcyclohexyl)sulfamide (80.0 mg, 0.20 mmol) and 3-bromobenzotrifluoride (56 μL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (98 mg, 90%) as a colorless solid, mp 119–121 °C: $[\alpha]^{23}_D$ -70 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.39 (m, 3H), 7.38–7.20 (m, 11H), 4.68 (d, *J* = 2.5 Hz, 1H), 4.65 (d, *J* = 4.7 Hz, 1H), 4.37–4.25 (m, 3H), 2.95 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.69 (dd, *J* = 14.0, 9.2 Hz, 1H), 2.17 (d, *J* = 11.7 Hz, 1H), 2.06 (dd, *J* = 14.6, 3.0 Hz, 1H), 1.83 (t, *J* = 13.2 Hz, 1H), 1.65–1.42 (m, 6H), 1.18 (q, *J* = 13.0 Hz, 1H), 1.00 (q, *J* = 13.0 Hz, 1H), 0.83 (q, *J* = 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 138.5, 137.8, 132.3, 130.96 (q, *J* = 32.5 Hz), 129.18, 128.6, 128.5, 128.1, 127.7, 127.1, 125.78 (q, *J* = 3.75 Hz), 124.14 (q, *J* =

270 Hz), 123.70 (q, *J* = 3.75 Hz), 63.9, 56.6, 50.7, 44.9, 40.5, 38.1, 31.1, 29.80, 25.3, 22.9, 22.6, 1 carbon signal is missing due to incidental equivalence; ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.65 (s); IR (neat) 1495, 1453, 1327, 1154, 1116, 1074 cm^{-1}. MS (ESI+) 543.2292 (543.2288 calcd for $C_{30}H_{33}F_3N_2O_2S$, M + H^+). The enantiopurity was determined to be 96.5:3.5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 6% IPA/Hexanes, 1.0 mL/min, λ 210 nm, RT= 15.4 and 18.9 min).



(S)-1,3-dibenzyl-4-(3-(4-fluorophenoxy)benzyl)-2-thia-1,3-diazaspiro[5.5]undecane 2,2-dioxide (Table 4.4, entry 12). The general procedure 5 was employed for the coupling of *N*-Benzyl-*N'*-benzyl-*N*-(1-allylcyclohexyl)sulfamide (80.0 mg, 0.20 mmol) and 3-Bromo-4′-fluorodiphenyl ether (107 mg, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (*S*)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (98 mg, 84%) as a colorless solid, mp 122–125 °C: $[\alpha]^{23}_D$ -65 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.43–7.38 (m, 4H), 7.34–7.28 (m, 4H), 7.26–7.20 (m, 3H), 7.04–6.99 (m, 2H), 6.92–6.88 (m, 2H), 6.85–6.81 (m, 2H), 6.67 (t, *J* = 2.0 Hz, 1H), 4.67 (dd, *J* = 16.5, 11.7 Hz, 2H), 4.31 (d, *J* = 15.7 Hz, 1H), 4.28–4.21 (m, 2H), 2.86 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.57 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.20–2.14 (m, 1H), 2.07 (dd, *J* = 14.6, 2.9 Hz, 1H), 1.74 (t, *J* = 14.1 Hz, 1H), 1.63–1.47 (m, 5H), 1.41 (d, *J* = 13.1 Hz, 1H), 1.17 (qt, *J* = 13.4, 3.7 Hz, 1H), 1.02 (qt, *J* = 13.8, 4.0 Hz, 1H), 0.84 (qt, *J* = 13.4, 4.6 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.9 (d, J_{CF} = 242.9 Hz), 157.9, 153.05 (d, J_{CF} = 3.5 Hz),

140.6, 139.6, 138.2, 130.1, 128.6, 128.5, 128.1, 127.5, 127.1, 127.0, 124.0, 120.45 (d, J_{CF} = 8.8 Hz), 119.1, 117.0, 116.5 (d, J_{CF} = 22.9 Hz), 63.8, 56.8, 50.4, 44.9, 40.7, 38.2, 31.0, 29.5, 25.3, 23.0, 22.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ –120.00– –120.07 (m); IR (neat) 1497, 1441, 1330, 1198, 1157, 1110 cm^{-1}. MS (ESI+) 585.2582 (585.2582 calcd for $C_{35}H_{37}FN_2O_3S$, M + H^+). The enantiopurity was determined to be 95.5:4.5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 6% IPA/Hexanes, 1.0 mL/min, λ 210 nm, RT= 24.6 and 33.5 min).

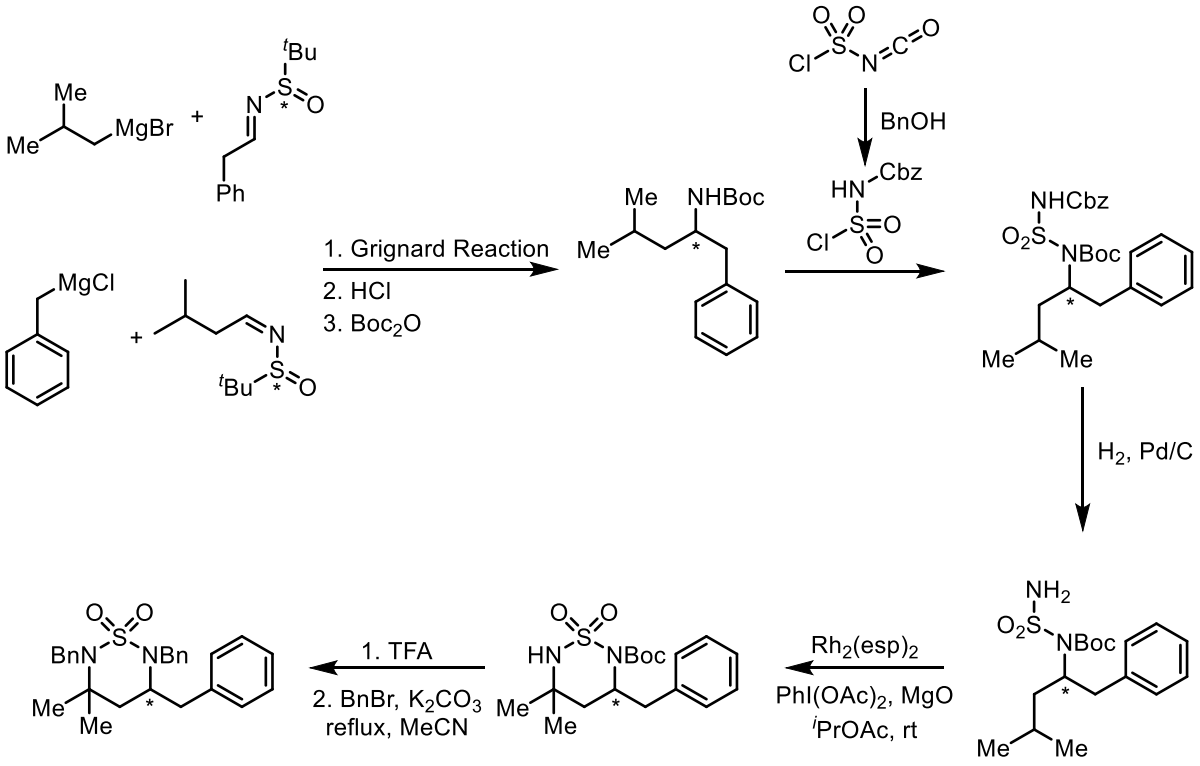


(S)-1,3-dibenzyl-4-(3-methoxybenzyl)-2-thia-1,3-diazaspiro[5.5]undecane 2,2-dioxide (Table 4.4, entry 13). The general procedure 5 was employed for the coupling of *N*-Benzyl-*N'*-benzyl-*N*-(1-allylcyclohexyl)sulfamide (80.0 mg, 0.20 mmol) and 3-bromoanisole (51 µL, 0.40 mmol) using a catalyst composed of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and (S)-SIPHOS-PE (5.1 mg, 0.010 mmol), sodium *tert*-butoxide (38.0 mg, 0.40 mmol), a reaction temperature of 120 °C, and a reaction time of 18 h in 1.6 mL of xylenes. This procedure afforded the title compound (89 mg, 88%) as a colorless solid, mp 141–144 °C: $[\alpha]^{23}_D$ -52 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.24 (q, J = 7.1 Hz, 0H), 7.17 (t, J = 7.9 Hz, 0H), 6.74 (dd, J = 8.2, 2.5 Hz, 0H), 6.70 – 6.66 (m, 0H), 6.60 (t, J = 2.0 Hz, 0H), 4.68 (dd, J = 16.4, 13.1 Hz, 0H), 4.29 (dd, J = 30.4, 16.6 Hz, 1H), 3.76 (s, 1H), 2.89 (dd, J = 13.5, 4.6 Hz, 1H), 2.58 (dd, J = 13.5, 10.3 Hz, 1H), 2.18 (d, J = 12.2 Hz, 1H), 2.09 (dd, J = 14.6, 2.6 Hz, 1H), 1.74 (t, J = 12.0 Hz 1H), 1.65–1.36 (m, 6H), 1.24–1.08 (m, 1H), 1.07–0.91 (m, 1H), 0.90–0.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 140.7, 139.1, 138.4,

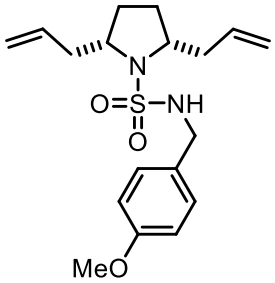
129.7, 128.6, 128.5, 128.1, 127.5, 127.1, 127.0, 121.4, 114.6, 112.5, 63.9, 56.9, 55.4, 50.4, 44.9, 41.0, 38.2, 31.1, 29.5, 25.3, 22.9, 22.6; IR (neat) 1584, 1496, 1452, 1327, 1150, 1111 cm^{-1}. MS (ESI+) 505.2523 (505.2519 calcd for $C_{30}H_{36}N_2O_3S$, M + H^+). The enantiopurity was determined to be 97:3 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 6% IPA/Hexanes, 1.0 mL/min, λ 210 nm, RT= 32.5 and 35.2 min).

Determination Of Absolute Configuration for 6-Membered Cyclic Sulfamides

The absolute configuration is currently under investigation. The following reaction sequence is being tested to generate an authentic sample for determining absolute configuration.



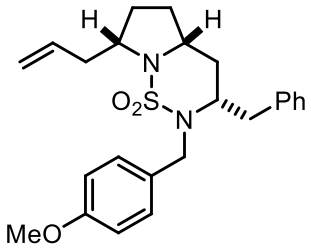
Desymmetrization of Sulfamides



(2S,5R)-2,5-diallyl-N-(4-methoxybenzyl)pyrrolidine-1-sulfonamide (4-47). The title compound was prepared by employing the following two-step procedure. A round-bottom flask equipped with a stir bar was charged with (±)-(*E*,2*R**,5*S**)-*tert*-butyl 2-allyl-5-[3-(trimethylsilyl)allyl]pyrrolidine-1-carboxylate (1.94 g, 6 mmol) and dichloroethane (30 mL, 0.2 M). Trifluoroacetic acid (6 mL, 1.0 M) was added to the flask and the mixture was stirred at reflux overnight. The solution was then concentrated in vacuo. Toluene was added and the resulting solution was concentrated in vacuo to remove any excess TFA. The crude amine (TFA salt) was used without additional purification.

A separate flame dried flask was charged with *N*-(4-methoxybenzyl)-2-oxooxazolidine-3-sulfonamide (1.89 g, 6.6 mmol), 4-dimethylaminopyridine (147 mg, 1.2 mmol), and a stirbar, then was evacuated and backfilledwith N_2. Acetonitrile (24 mL) was added, followed by Et_3N (2.3 mL, 16.5 mmol)), and then the reaction vessel was placed in an oil bath at 75 °C. The appropriate amine TFA salt as prepared above was added and the resulting mixture was stirred at 75 °C overnight (approximately 16 hours). The mixture was cooled to rt, solvent was removed via rotary evaporation, and the residue was partitioned between CH_2Cl_2 and 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, and the resulting residue

was purified by flash chromatography on silica gel. This procedure afforded the title compound (1.58 g, 75%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.78 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 2H), 5.12–5.03 (m, 4H), 4.23 (s, 1H), 4.18 (s, 2H), 3.90–3.82 (m, 2H), 3.80 (s, 3H), 2.55 (dddd, *J* = 12.4, 6.9, 3.5, 1.4 Hz, 2H), 2.30–2.18 (m, 2H), 1.90 (ddt, *J* = 10.9, 7.4, 5.2 Hz, 2H), 1.78–1.68 (m, 2H).



(3S,4aR,7S)-7-allyl-3-benzyl-2-(4-methoxybenzyl)hexahydro-2H-pyrrolo[1,2-b][1,2,6]thiadiazine 1,1-dioxide (4-48). An oven-dried test tube was cooled under a stream of nitrogen and charged with (2*S*,5*R*)-2,5-diallyl-*N*-(4-methoxybenzyl)pyrrolidine-1-sulfonamide**,** $Pd(OAc)_2$ (0.9 mg, 4 mol%), chiral ligand (4 mol%), phenyl triflate (45 mg, 0.2 mmol), and LiO^tBu (16 mg, 0.5 mmol). The tube was purged with nitrogen, then either ^{t}BuOH or $PhCF_3$ (1 mL, 0.25 M) was added via syringe. The mixture was heated to 82 °C or 100 °C with stirring for 16 h. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (1 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were dried over anhydrous Na_2SO4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.31 (d, *J* = 8.4 Hz, 2H), 7.25–7.22 (m, 2H), 7.22–7.17 (m, 1H), 7.11–7.07 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.80 (ddt, *J* = 17.3, 10.2, 7.0 Hz, 1H), 5.14–5.05 (m, 2H), 4.54 (d, *J* = 16.3 Hz, 1H), 4.28 (td, *J* = 11.4, 10.3, 4.2 Hz, 1H), 3.94 (d, *J* = 16.4 Hz, 1H), 3.78 (s, 3H), 3.74 (dq, *J* = 8.8, 4.8, 4.0 Hz, 1H), 3.25 (ddt, *J* = 11.3, 4.9, 3.4 Hz, 1H), 2.89 (dd, *J* = 13.4, 4.5 Hz, 1H), 2.64–2.57 (m, 1H), 2.54 (dd, *J* = 13.4, 10.7 Hz, 1H), 2.44–2.36 (m, 1H), 1.91–1.79 (m, 2H), 1.71–1.63 (m, 2H), 1.51–1.40 (m, 2H). The enantiomeric excess for compounds in **Scheme 4.13** and **Scheme 4.15** were determined by chiral HPLC analysis (Chiralcel ADH, 0.46 cm x 25 cm, 10% iPrOH/hexanes, 0.8 mL/min, RT = 20.4 and 22.5 min). *The absolute configuration has not been determined at this point.*

4.12 References

(1) Mai, D.N.; Wolfe, J.P. *J. Am. Chem. Soc.* **2010**, *132*, 12157.

(2) (a) Hopkins, B.A.; Wolfe, J.P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9886; (b) Babij, N.R.; Wolfe, J.P. *Angew. Chem. Int. Ed.* **2013**,*52*, 9247.

(3) Hopkins, B.A.; Wolfe, J.P. *Chem. Sci.* **2014**, *5*, 4840.

(4) Fu, W.; Tang, W. *ACS Catal*. **2016**, *6*, 4814.

(5) Kočovský, P.; Bäckvall, J. -E. *Chem. Eur. J.* **2015**, *21*, 36.

(6) Borghese, A.; Antoine, L.; Van Hoeck, J. P.; Mockel, A.; Merschaert, A. *Org. Process Res. Dev*. **2006**, *10*, 770.

(7) Weinstein, A.B.; Stahl, S.S. *Angew. Chem. Int. Ed.* **2012**, *51*, 11505.

(8) Babij, N.R.; McKenna, G.M.; Fornwald, R.M.; Wolfe, J.P. *Org. Lett.* **2014**, *16*, 3412.

(9) Aranyos, A.; Old, D.W.; Kiyomori, A.; Wolfe, J.P.; Sadighi, J.P.; Buchwald, S.L. *J. Am. Chem. Soc*. **1999**, *121*, 4369.

(10) Rousseaux, S.; García-Fortanet, J.; Sanchez, M. A. Del Aguila; Buchwald, S.L. *J. Am. Chem. Soc.*, **2011**, *133*, 9282.

(11) Zhu, Ye; Buchwald, S.L. *J. Am. Chem. Soc.* **2014**, *136*, 4500.

(12) (a) Huan, Z.; Liu, Z.; Zhou, J. *J. Am. Chem. Soc.* **2011**, *133*, 15882; (b) Jiao, Z.; Beiger, J.J.; Jin, Y.; Ge, S.; Zhou, J.; Hartwig, J.F. *J. Am. Chem. Soc.* **2016**, *138*, 15980.

(13) Garlets, Z.J.; Parenti, K.R.; Wolfe, J.P. *Chem. Eur. J.* **2016**, *22*, 5919.

(14) McDonald, R.I.; Stahl, S.S. *Angew. Chem.* **2010**, *122*, 5661; *Angew. Chem. Int. Ed.* **2010**, *49*, 5529.

(15) Fornwald, R.M.; Fritz, J.A.; Wolfe, J.P. *Chem. Eur. J.* **2014**, *20*, 8782.

(16) Hopkins, B.A.; Wolfe, J.P. *Angew. Chem. Int. Ed*. **2012**, *51*, 9886; *Angew Chem.* **2012**, *124*, 10024.

(17) Ordóñez, M.; de la Cruz-Cordero, R.; Quiñónes, C.; González-Morales, A. *Chem. Commun*. **2004**, 672.

(18) Fekner, T.; Müller-Bunz, H.; Guiry, P.J. *Org. Lett*. **2006**, *8*, 5109.

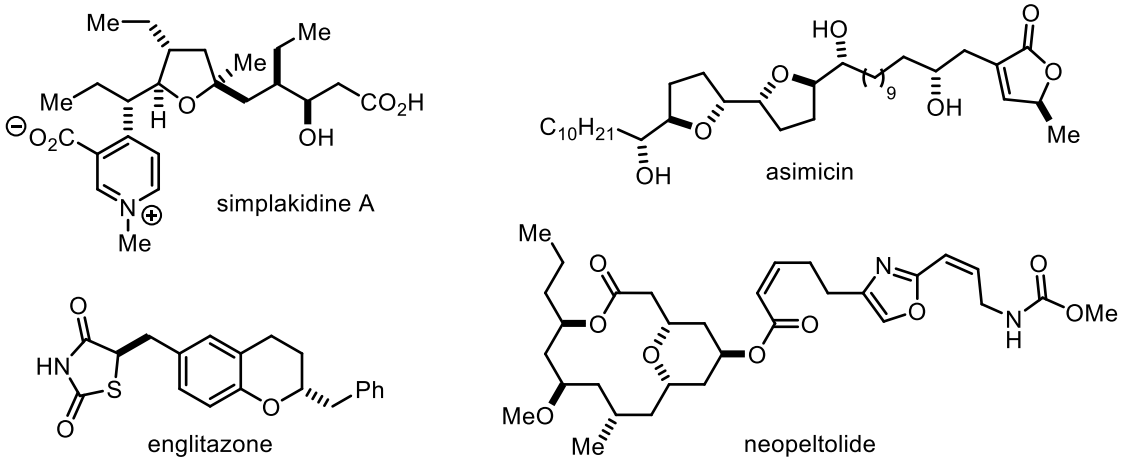
Chapter 5

Synthesis of Cyclic Ethers Via Metal-Catalyzed Alkene Difunctionalization Reactions

5.1 Background

New catalytic reactions which functionalize olefins have been extensively targeted for the development of oxidation, hydroformylation, and polymerization reactions. For example, the venerable Wacker oxidation functionalizes an olefin by oxidation in the presence of water and a Pd catalyst.[1] Transition metal catalysis remains a powerful area of organic chemistry for the expedient formation of new carbon-carbon bonds and carbon-heteroatom bonds.

Figure 5.1 Examples of Cyclic Ethers in Natural Products



Efforts in transition metal catalysis towards the synthesis of cyclic ethers is also an important area of research because cyclic ethers are commonly occurring elements in natural products and biologically active molecules. Specifically, cyclic ether substructures can be found in lignans, polyether ionophores, macrodiolides, and marine polyether terpenes.[2] The synthesis of tetrahydrofurans has been reviewed previously.[3] In the chapter below, several recent developments in the synthesis of tetrahydrofurans (5-membered cyclic ethers), as well as other cyclic ethers, are described. This summary is not meant to be comprehensive, but instead will give a flavor of the current research in the functionalization of olefins by carboalkoxylation reactions.

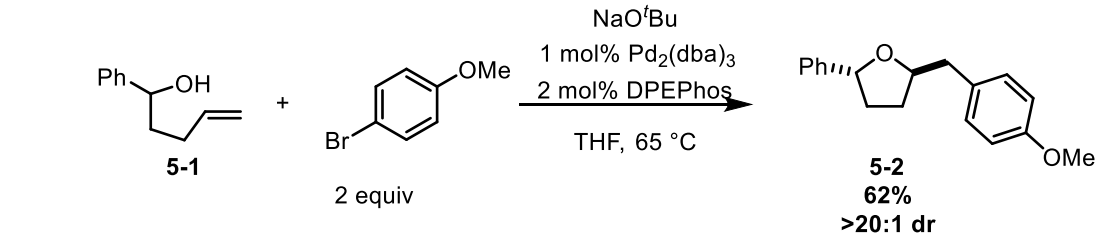
5.2 Metal-Catalyzed Carboalkoxylation of Olefins

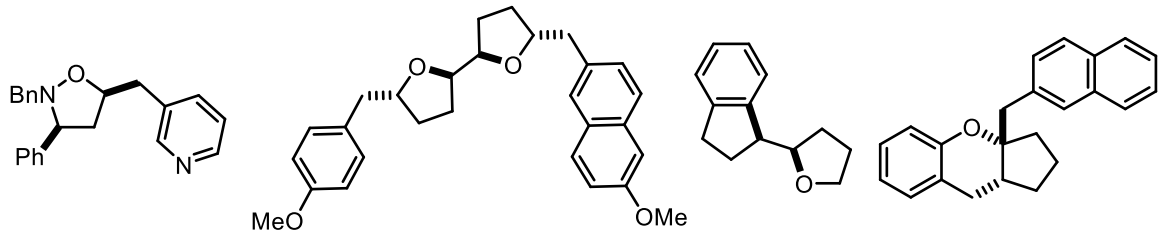
The Pd-catalyzed carboalkoxylation reaction of olefins tethered to an olefin has been widely investigated by the Wolfe group.[4] Building off pioneering reports by Semmelhack,[5] Wolfe and coworkers reported the first carboalkoxylation reaction in 2004 which achieves carbon-oxygen bond formation along with sp^3 carbon-sp^2 carbon bond formation.[4a] Since then, the substrate scope of this reaction has broadened to include new syntheses of isoxazolidines, attached-ring *bis*-tetrahydrofurans, 2-indan-1-yltetrahydrofuran, and chromans as shown in **Scheme 5.1**. Many of these reactions undergo a key *syn*-oxypalladation step which enables the products to be obtained in high diastereoselectivity.

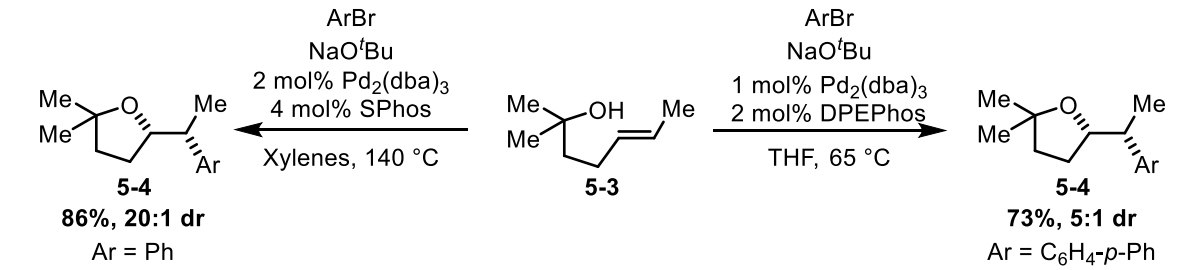
The expansion and improvement of substrate scope for this reaction has required the invention of new catalysts. For example, initial carboalkoxylation reactions of 1,2-

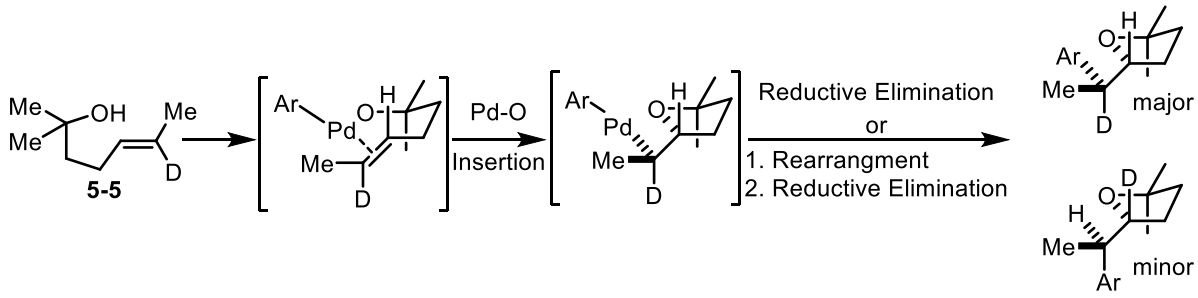
trans substituted alkenes unveiled a deleterious mechanistic pathway (reversible β-hydride elimination/insertion) which scrambled the stereocenters that were formed. This resulted in low diastereoselectivity. Therefore, the invention of a new catalyst (shown in **Scheme 5.1** using SPhos as ligand at elevated temperatures) was required for achieving carboalkoxylation reactions with high diastereoselectivity. Continued improvements to carboalkoxylation reactions will require the development of new catalysts and ligands.

Scheme 5.1 Pd-Catalyzed Carboalkoxylation Reactions





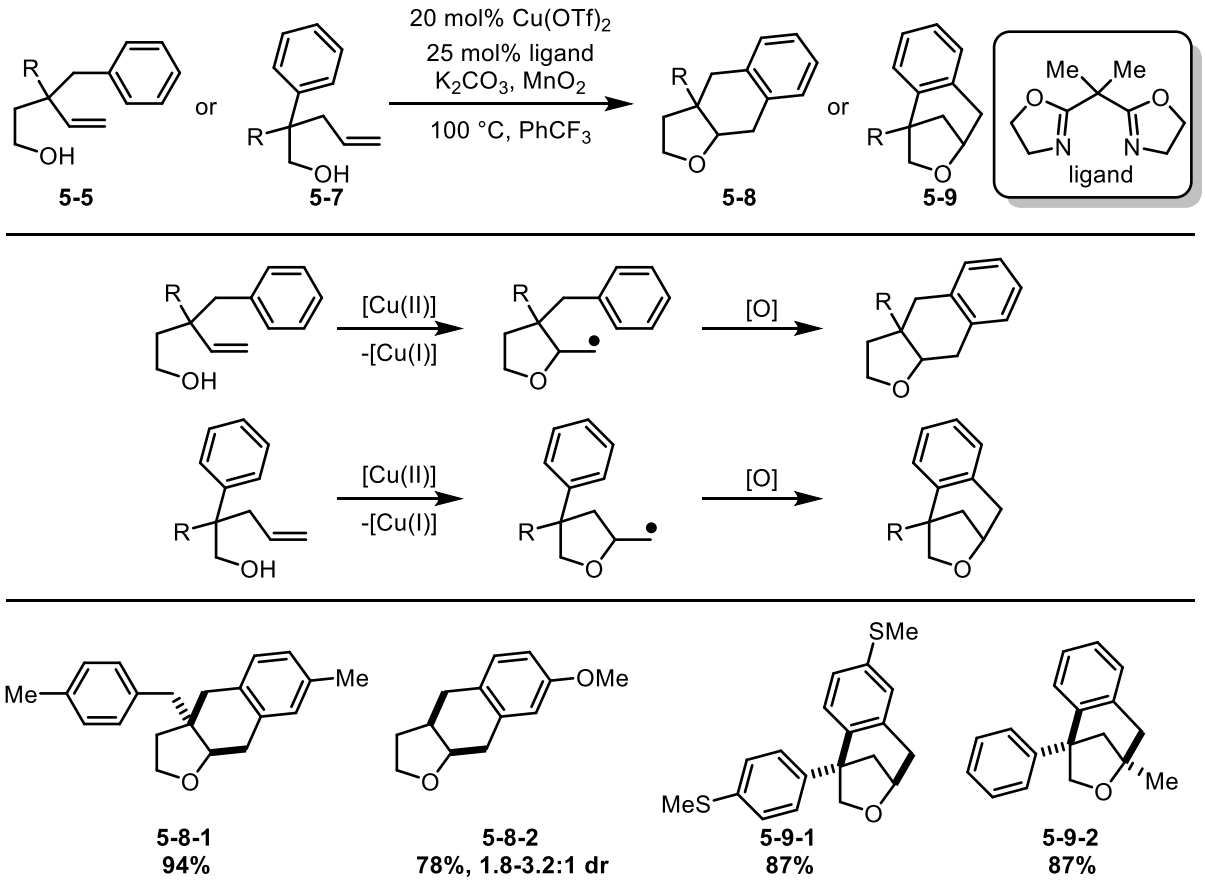




A copper-catalyzed synthesis of fused-ring and bridged-ring tetrahydrofurans by intramolecular carboetherification was demonstrated by Chemler and coworkers (**Scheme 5.2**).[6] The reaction proceeds by initial *syn*-oxycupration followed by homolytic cleavage of the akyl-cuprate to form a primary radical. The radical rapidly undergoes intramolecular addition to a tethered aryl ring. After further oxidation, the new polycyclic

tetrahydrofuran is formed. The reaction proceeds in good yields for a variety of different heterocycles, although the diastereoselectivity is modest at best.

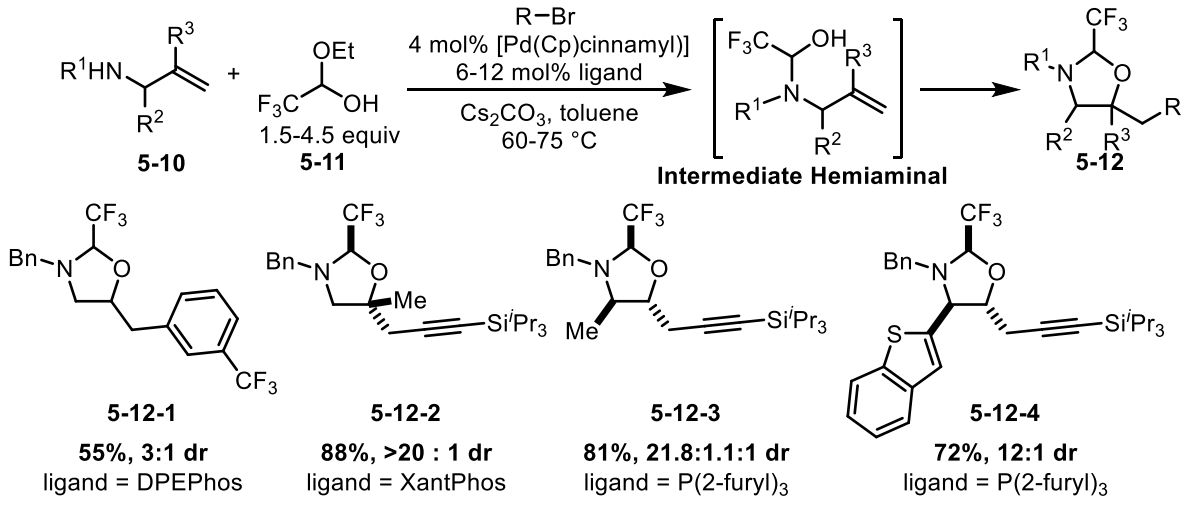
Scheme 5.2 Cu-Catalyzed Carboalkoxylation Reactions



A novel Pd-catalyzed sequence for the synthesis of amino alcohols has been recently developed by Waser and coworkers (**Scheme 5.3**).[7] This reaction describes a new strategy which uses **5-11** as a nucleophilic tether which enables the carboetherification reaction. The reaction is tolerant of a wide variety of electrophiles and allylamines, although different ligands were required for optimal results depending

on electrophile and allylamine. Notably, the reaction proceeds in >20:1 dr for the synthesis of **5-12-2** which is derived from a 1,1-disubstituted alkene. The reaction has yet to be rendered enantioselective, although an asymmetric variant of this strategy would be a welcome addition to this field. The amino alcohols are useful compounds because they contain orthogonally protected functional groups which can be unveiled by further manipulation.

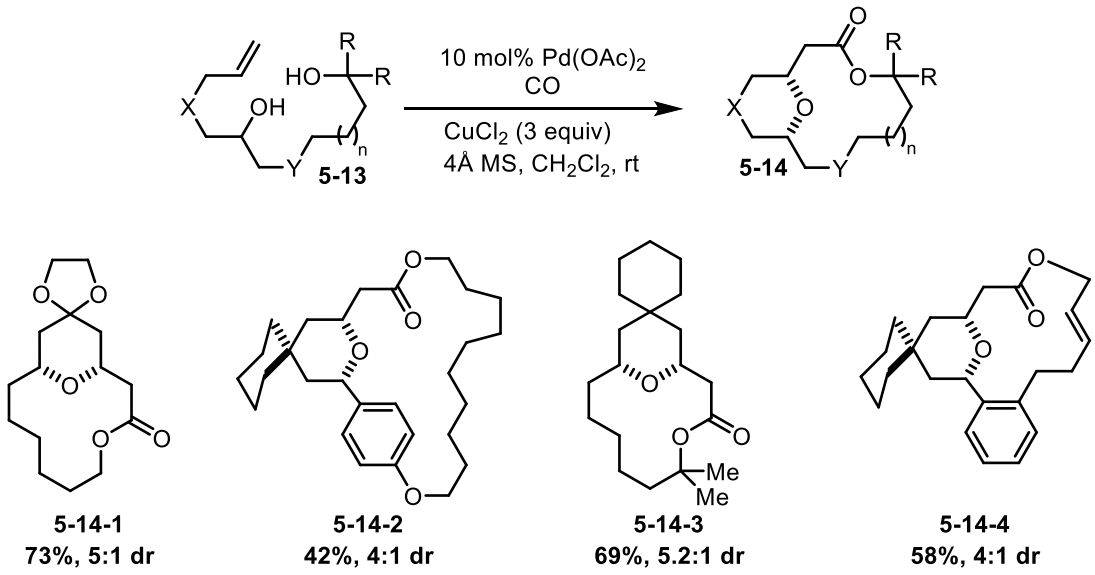
Scheme 5.3 One-Pot Pd-Catalyzed Alkoxylation Reaction for the Synthesis of Amino Alcohols



Recent work from the Dai group has provided a new Pd-catalyzed alkoxycarbonylative macrolactonization reaction (**Scheme 5.4**).[8] Many important macrocyclic compounds contain tetrahydropyran and tetrahydrofuran components embedded within the macrocycle. As such, a new alkene difunctionalization reaction

which achieves both cyclic ether formation and macrocycle formation in one step is an attractive disconnection to target. The Dai group has found that use of $Pd(OAc)_2$ as a catalyst in the presence of carbon monoxide and 3 equiv of copper (II) chloride can achieve this lofty goal. The reaction is competent for the formation of a variety of macrocycles with good yield and moderate diastereoselectivity. Different size macrocycles can be formed, and the backbone of the macrocycle can contain different functional groups like phenol ethers or olefins.

Scheme 5.4 Pd-Catalyzed Alkoxylation/Carbonylation for the Synthesis of Macrolactones



While carboalkoxylation reactions have been developed in many instances for racemic transformations, asymmetric reactions are also needed. Described in the upcoming section are the recent efforts towards this end.

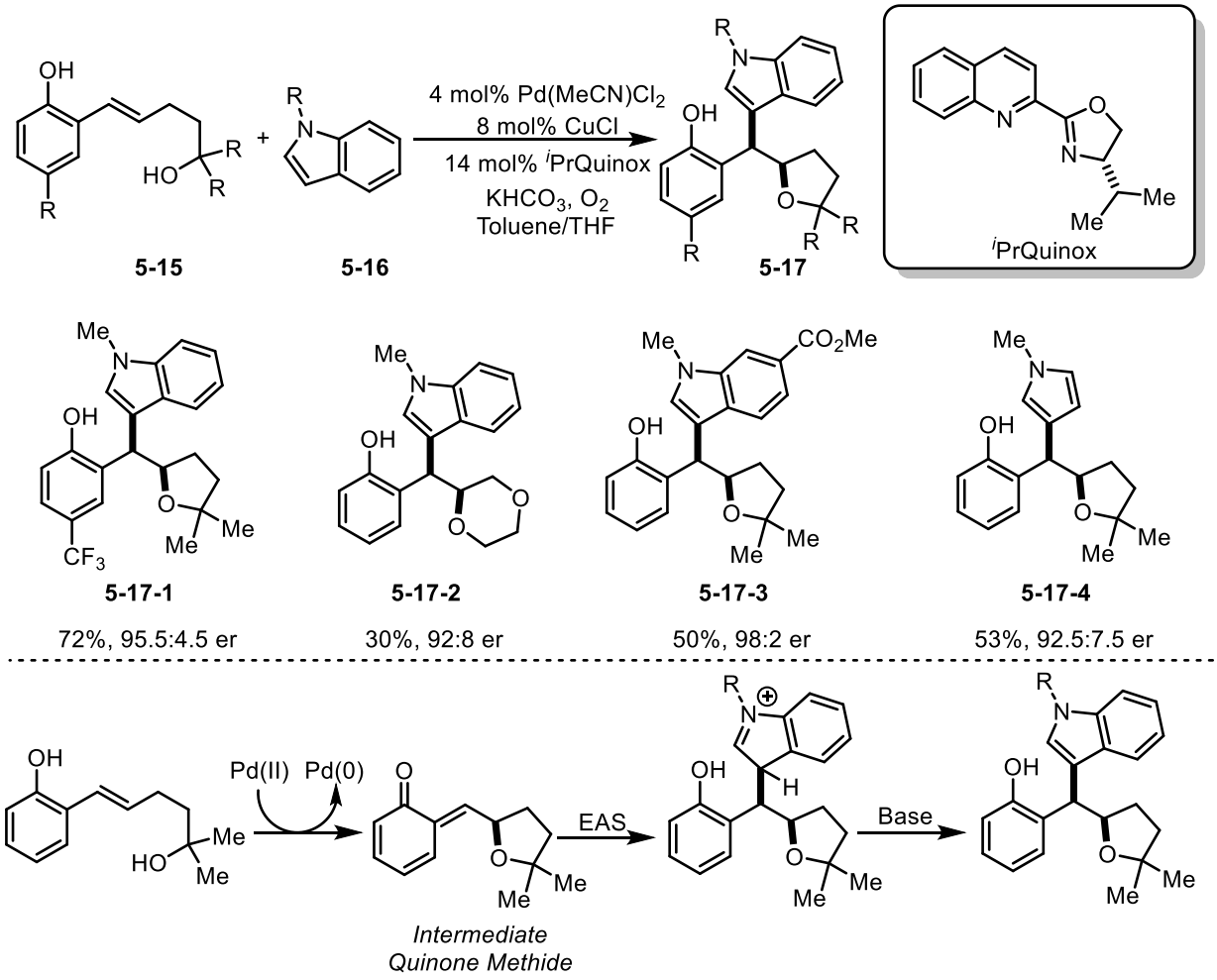
5.3 Asymmetric Metal-Catalyzed Carboalkoxylation of Olefins

The use of chiral catalysts for the asymmetric functionalization of olefins is an important area of research because unsaturated functional groups are especially situated for forging new carbon-carbon and carbon-heteroatom bonds. In addition, enantiopure compounds are highly desirable compounds in the pharmaceutical industry because only one enantiomer is therapeutically relevant (and sometimes the other exhibits dangerous properties). The topic of asymmetric Pd-catalyzed functionalization of olefins has been reviewed before,[9] and described below are a few examples of recent developments in enantioselective metal-catalyzed carboalkoxylation reactions.

Sigman expanded the scope of nucleophiles for enantioselective difunctionalization reactions developed in their lab[10] by examining indole as a nucleophile.[11] High levels of enantioselectivity are obtained by the use of ^{i}PrQuinox as a ligand. As shown in **Scheme 5.5**, different substituted indoles and pyrroles can be utilized in this reaction to obtain enantiomeric ratios up to 98:2. Perhaps the only unsatisfactory aspect of this reaction is the use of 15 equiv of nucleophile. The reaction proceeds through an intermediate quinone methide that is generated by intramolecular nucleopalladation with Pd(II). The quinone methide is trapped by the indole via electrophilic aromatic substitution (EAS) and ultimately re-aromatized by deprotonation to form the difunctionalized products. This reaction is also unique in that the Pd catalyst

is only used to build the carbon-oxygen bond, and not both bonds, during the course of the functionalization of the olefin. In this regard, without the phenol, it is unlikely that this reaction would be operative.

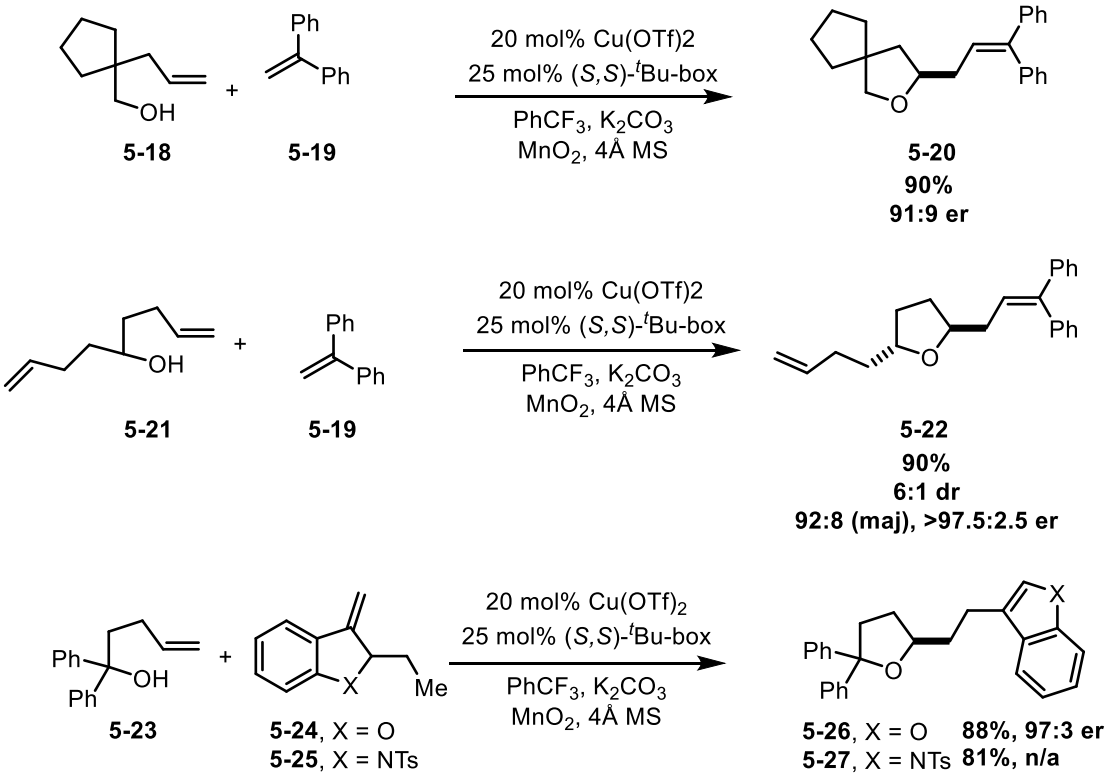
Scheme 5.5 Pd-Catalyzed Difunctionalization of Olefins with Indole as Nucleophile



The Chemler group recently demonstrated the first asymmetric carboetherification reaction of unactivated alkenes using a chiral copper catalyst

(**Scheme 5.6**).[12] The reaction is successful with 20 mol% copper(II) triflate and 25 mol% (*S*,*S*)-^{t}Bu-box ligand, and it likely proceeds through radical intermediates akin to the other transformations developed by the Chemler group.[6] The radical nature of the reaction also explains the use of radical acceptors derived from styrene and its derivatives for functionalizing the olefin by formation of a new carbon-carbon bond. The high enantioselectivity imparted by the chiral catalyst is achieved because of the concerted *syn*-alkoxycupration step in which the alkoxy-cuprate adds in a concerted fashion across the double bond. After this occurs, homolytic cleavage produces a primary radical which can add intramolecularly to tethered aryl rings or intermolecularly to radicalphiles in solution.

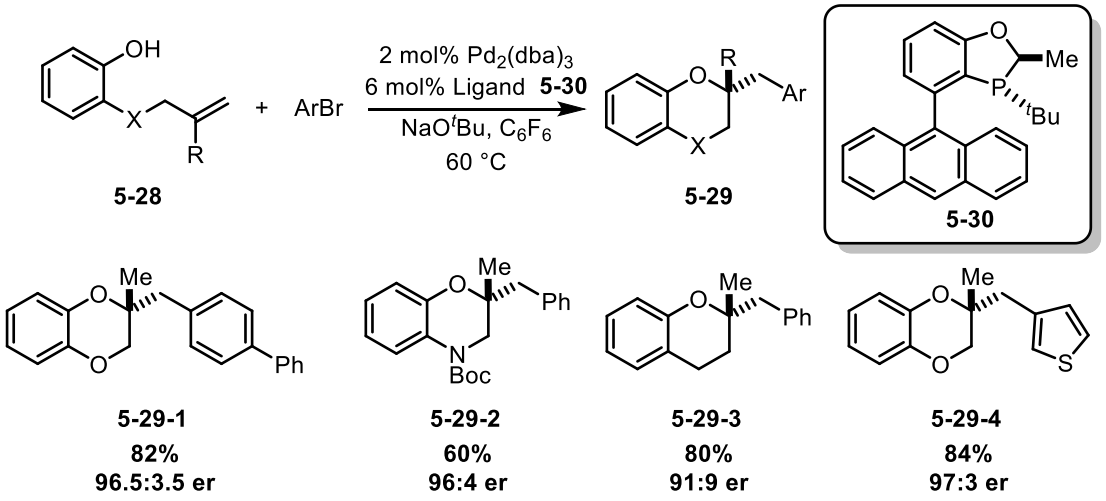
Scheme 5.6 Asymmetric Cu-Catalyzed Difunctionalization of Olefins



Recently, Tang and coworkers utilized a new Pd catalyst with a P-chiral ligand to perform asymmetric carboalkoylation reactions for the synthesis of chromans and 1,4-dioxanes (**Scheme 5.7**).[13] High levels of enantio-induction were achieved with ligand **5-30** at 60 °C with hexafluorobenzene solvent. Importantly, hexafluorobenzene solvent was required for achieving greater than 90:10 er. The reaction performs most efficiently for 1,1-disubstituted alkenes due to competing formation of undesired Heck arylation products which the authors isolate and identify in this work. The reaction proceeds in up to 97.5:2.5 er and up to 85% yield. The synthesis of chromans like **5-29-3** suffered from lower enantioselectivity suggesting that the heteroatom in the backbone is important for

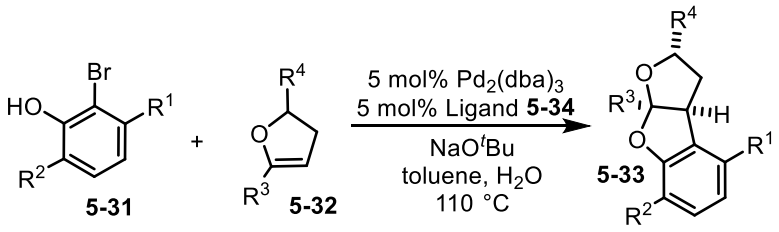
high enantio-induction. Also, cyclization to form benzofurans was achieved albeit in low enantioselectivity (57.5:42.5 er, *not shown*).

Scheme 5.7 Asymmetric Pd-Catalyzed Synthesis of 1,4-Dioxanes and Chromans

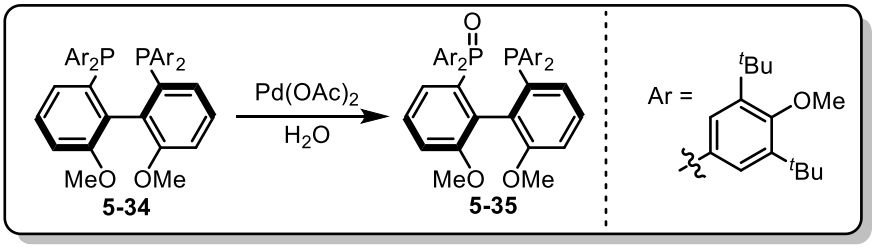


A novel Pd-catalyzed intermolecular carboetherification of dihydrofurans was developed by Mazet and coworkers (**Table 5.1**).[14] This unique reaction differs from many of the reactions described above in that the electrophile is tethered to the nucleophile, a strategy reminiscent of the Larock indole synthesis.[15] The reaction can be accomplished asymmetrically using chiral ligand **5-34** which is generated in situ with the addition of water. The reaction achieves the synthesis of a variety of fused tetrahydrofurobenzofurans in excellent dr (>20:1 dr) and good enantiomeric excess (up to 97% ee).

Table 5.1 Pd-Catalyzed Enantioselective Carboetherification of Dihydrofurans



R^1	R^2	R^3	R^4	Yield (%)	dr	ee (%)
H	H	H	H	74	>20:1	92
OMe	H	H	H	42	>20:1	57
H	OMe	H	H	89	>20:1	88
H	H	Me	H	64	>20:1	91
H	H	H	*p*-Tol	67	49:1	91



5.4 Conclusion

Despite remarkable developments in the synthesis of cyclic ethers, only recently has the synthetic community been able to invent catalysts which achieve asymmetric carboalkoxylation reactions of unactivated alkenes. Beginning with the work of the Chemler group in 2014, the synthetic community has witnessed several unique contributions to the field of asymmetric alkene difunctionalization reactions including the work described in the next chapter. The next chapter describes the development of a new chiral TADDOL phosphite ligand which enables the carboalkoxylation of olefins with a Pd catalyst.

5.5 References

(1) Jira, R. *Angew. Chem. Int. Ed*. **2009**, *48*, 9034.

(2) (a) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep*. **2005**, 696; (b) Faul, M. M.; Huff, B. E. *Chem. Rev*. **2000**, *100*, 2407; (c) Kang, E. J.; Lee, E. *Chem. Rev*. **2005**, *105*, 4348; (d) Fernández, J.J.; Souto, M.L.; Norte, M. *Nat. Prod. Rep*. **2000**, *17*, 235.

(3) Wolfe, J.P.; Hay, M.B. *Tetrahedron*, **2007**, *63*, 261.

(4) (a) Wolfe, J.P.; Rossi, M.A. *J. Am. Chem. Soc*. **2004**, *126*, 1620; (b) Hay, M.R.; Hardin, A. R.; Wolfe, J.P. *J. Org. Chem*. **2005**, *70*, 3099; (c) Hay, M.R.; Wolfe, J.P. *J. Am. Chem. Soc*. **2005**, *127*, 16468; (d) Hay, M.R.; Wolfe, J.P. *Tetrahedron Lett*. **2006**, *47*, 2793; (e) Nakhla, J.S.; Kampf, J.W.; Wolfe, J.P. *J. Am. Chem. Soc*. **2006**, *128*, 2893; (f) Hay, M.R.; Wolfe, J.P. *Angew. Chem. Int. Ed*. **2007**, *46*, 6492; (g) Lemen, G.S.; Giampietro, N.C.; Hay, M.B.; Wolfe J.P. *J. Org. Chem*. **2009**, *74*, 2533; (h) Ward, A.F. Wolfe, J.P. *Org. Lett*. **2010**, *12*, 1268; (i) Ward, A.F.; Xu, Y.; Wolfe, J.P. *Chem. Commun*. **2012**, *48*, 609.

(5) (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc*. **1984**, *106*, 1496; (b) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem*. **1990**, *62*, 2035; (c) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett*. **1993**, *34*, 7205; (d) Mikami, K.; Shimizu, M. *Tetrahedron*, **1996**, *52*, 7287.

(6) Miller, Y.; Miao, L.; Hosseini, A.S.; Chemler, S.R. *J. Am. Chem. Soc.* **2012**, *134*, 12149.

(7) Orcel, U.; Waser, J. *Angew. Chem.* **2015**, *127*, 5339; *Angew. Chem. Int. Ed.* **2015**, *54*, 5250.

(8) Bai, Y.; Davis, D.C.; Dai, M. *Angew. Chem.* **2015**, *126*, 6637; Bai, Y.; Davis, D.C.; Dai, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6519.

(9) (a) McDonald, R.I.; Liu, G.; Stahl, S.S. *Chem. Rev.* **2011**, *111*, 2981; (b) Sun, Y.-w.; Zhu, P.-l.; Xu, Q.; Shi, M. *RSC Adv*. **2013**, *3*, 3153.

(10) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc*. **2009**, *131*, 17074.

(11) Pathak, T.P.; Gligorich, K.M.; Welm, B.E.; Sigman, M.S. *J. Am. Chem. Soc.* **2010**, *132*, 7870.

(12) Bovino, M.T.; Liwosz, T.W.; Kendel, N.E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S.R. *Angew. Chem. Int. Ed*. **2014**, *53*, 6383.

(13) (a) Hu, N.; Li, Ke.; Wang, Z.; Tang, W. *Angew. Chem. Int. Ed*. **2016**, *55*, 5044; (b) Hu, N.; Li, Ke.; Wang, Z.; Tang, W. *Angew. Chem.* **2016**, *128*, 5128.

(14) Borrajo-Calleja, G.M.; Bizet, V.; Mazet, C. *J. Am. Chem. Soc.* **2016**, *138*, 4014.

(15) Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.

Chapter 6

Asymmetric Synthesis of Tetrahydrofurans by a Pd-Catalyzed Alkene Difunctionalization Reaction

6.1 Introduction

Cyclic ethers with substitution at C2 are widely prevalent in many biologically active compounds.[1] Due to the high prevalence of this functional group motif, considerable effort has been targeted at the development of methods for the asymmetric synthesis of cyclic ethers.[2] Previous reports from the Wolfe group detail the development of a Pd-catalyzed carboalkoxylation reaction between γ-hydroxyalkenes and aryl or alkenyl halides which produce C2-substituted tetrahydrofurans with high diastereoselectivity.[3] Even though this reaction was developed over 10 years ago, the enantioselective variant of this reaction has remained undeveloped until recently.

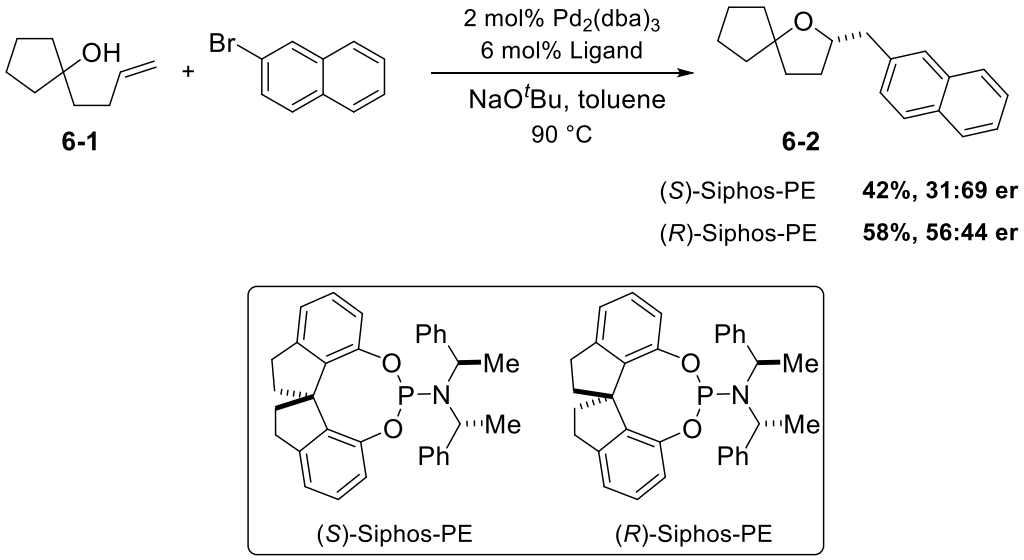
While many groups have demonstrated successful asymmetric carboamination reactions, the corollary developments for the asymmetric synthesis of cyclic ethers has been slower to develop. Nitrogen atoms hold a distinct advantage over oxygen atoms in that a protecting group can be used to modulate the electronics and sterics of the nitrogen atom while maintaining nucleophilicity. Because oxygen is divalent, it does not have this same capacity. Therefore, the development of an asymmetric carboalkoxylation reaction relies primarily on the chiral environment of the catalyst, and

not on substrate electronic manipulations. Efforts towards the development and use of a new chiral ligand for Pd-catalyzed carboalkoxylation reactions are described below.

6.2 Asymmetric Synthesis of Tetrahydrofurans

The reaction design for an asymmetric carboalkoxylation reaction took into account earlier developments for the enantioselective cyclization of ureas and sulfamides which demonstrated that subtle steric and electronic protecting group manipulations of the nitrogen atoms of the sulfamide strongly altered the enantioselectivity. While oxygen nucleophiles lack this opportunity for substrate control, the same catalyst conditions could induce desirable asymmetry since the reactions operate under the same Pd mechanism. Regrettably, the use of chiral phosphoramidites (*R*)-Siphos-PE and (*S*)-Siphos-PE failed to achieve synthetically useful enantiomeric ratios despite obtaining decent yields (**Scheme 6.1**). Without a protecting group handle to influence the substrates, the development of a new ligand was explored as a solution to developing an asymmetric carboalkoxylation reaction.

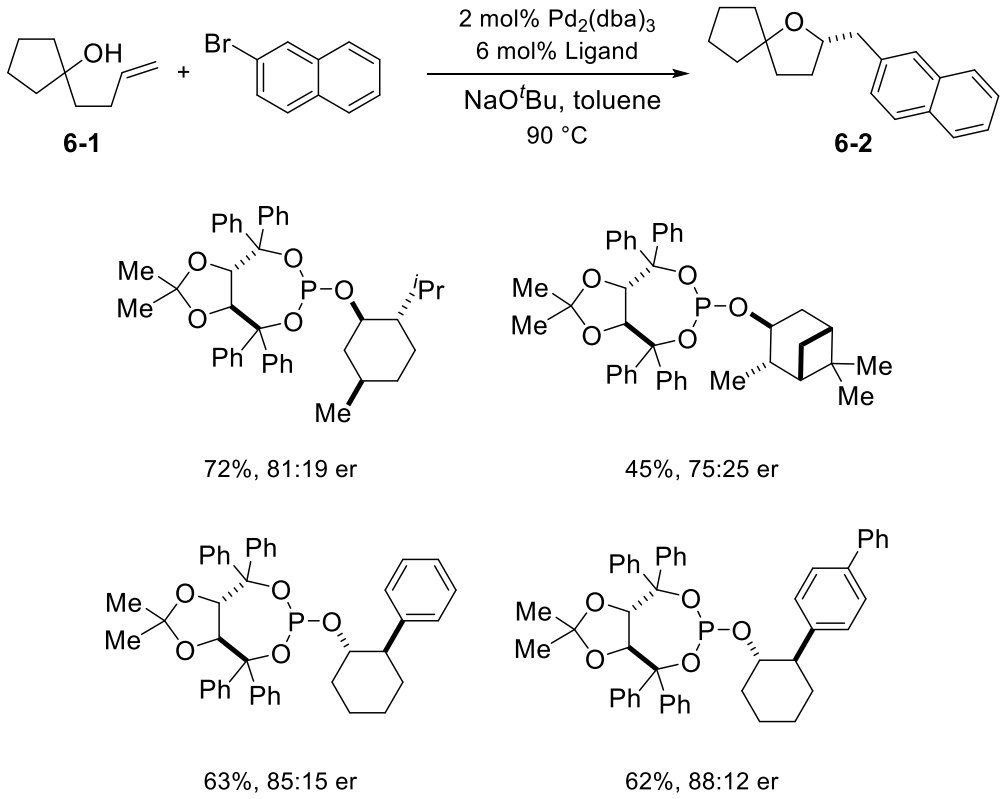
Scheme 6.1 Evaluation of Chiral Phosphoramidites for Asymmetric THF Synthesis



Chiral phosphites with TADDOL backbones were considered as a possible modular scaffold for this purpose. The TADDOL backbone was selected as a potential scaffold because it bore similar electronics to chiral phosphoramidites which demonstrated decent yields but poor enantioselectivity. The TADDOL backbone is an attractive scaffold because it can easily be altered for tuning the ligand. For example, the ketal can be deprotected or alkylated in different ways, or different aryl rings can be incorporated by Grignard addition to the ester precursor. Secondly, different alcohols or amines can be incorporated during ligand synthesis. In this regard, synthesis of the ligands is performed by simply combining the TADDOL backbone with PCl_3, and then adding the secondary component of the desired ligand. Finally, the ligands are stable, and they perform with the same capacity after two years storage in a dessicator. The development and optimization of the new chiral TADDOL ligand has been described and is summarized in **Scheme 6.2**.[4]

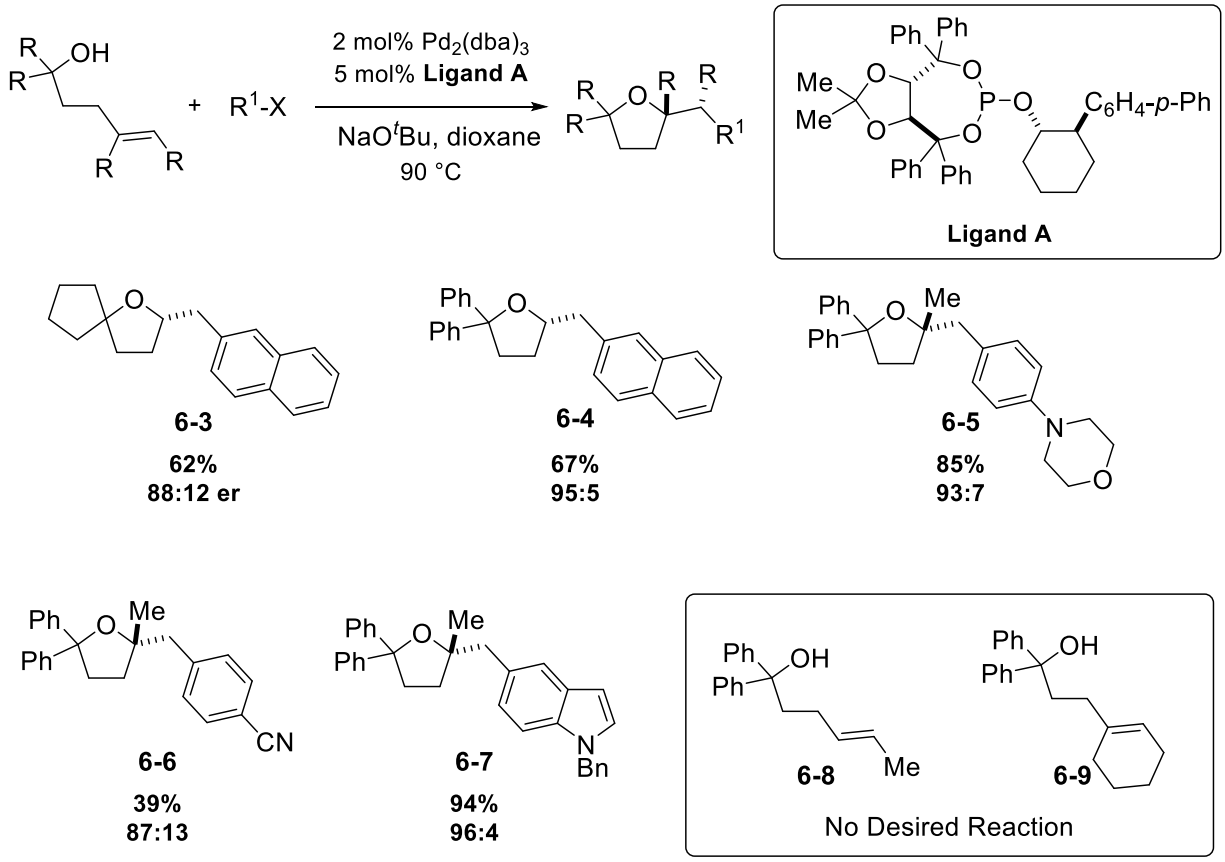
The ligand development unveiled important factors for inducing asymmetry. First, substitutions in the backbone either at the ketal ring or with the phenyl groups failed to improve the enantioselectivity, but phosphites derived from TADDOL, PCl_3, and chiral cyclohexanol derivatives gave promising results. Initial experimentation with naturally occurring alcohols like menthol and isopinocampheol as consitutents of the ligand exhibited synthetically useful enantiomeric ratios (up to 81:19 er as shown in **Scheme 6.2**). Further investigation of the substitution pattern demonstrated that increases in steric bulk of the chiral cyclohexanol improved the enantioselectivity. The model reaction was able to achieve 88:12 er by using a ligand bearing a chiral cyclohexanol with biphenyl substitution.

Scheme 6.2 Ligand Development for Asymmetric Carboalkoxylation Reaction



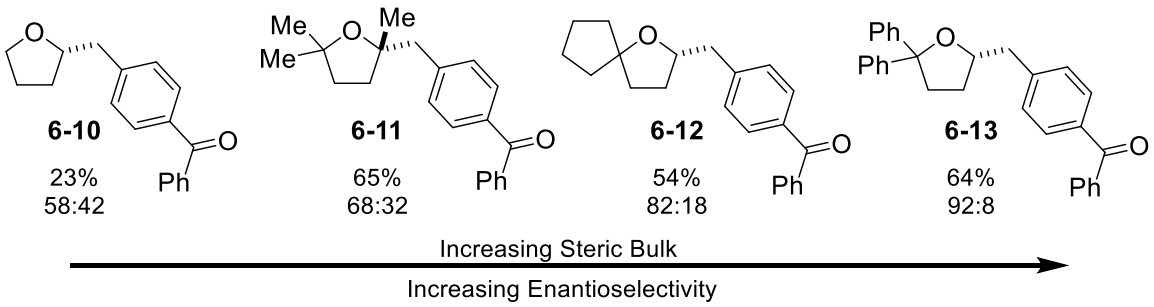
After the ligand structure was optimized, the substrate scope was evaluated. A wide variety of electrophiles were competent for the reaction as shown in **Scheme 6.3**. These include electron-rich electrophiles as shown for product **6-5** and electron poor electrophiles as shown for **6-6**. In addition, a Bn-protected indole was successfully incorporated in the synthesis of **6-7**. 1,1-Disubstituted alkenes were tolerated by this reaction, but at this point the use of substrates bearing internal alkenes like **6-8** or **6-9** have not produced desirable results.

Scheme 6.3 Substrate Scope for Asymmetric Carboalkoxylation Reaction



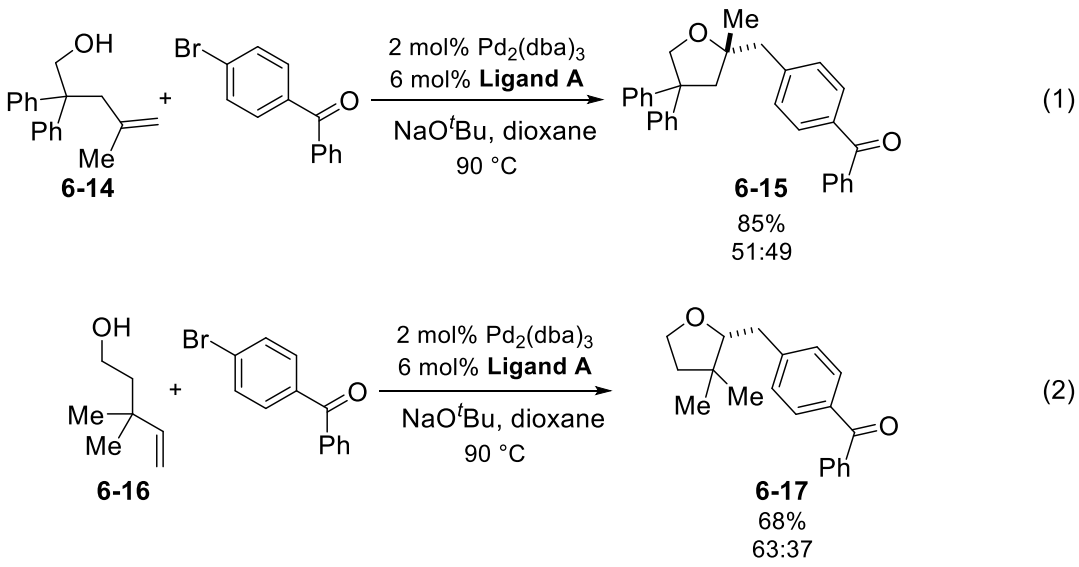
During the investigation, it was discovered that the steric bulk next to the oxygen nucleophile had a significant influence on enantioselectivity. As shown in **Figure 6.1**, the enantioselectivity advances with increasing steric bulk from hydrogen to phenyl from 58:42 for **6-10** up to 92:8 for **6-13** when 4-bromobenzophenone is used as electrophile.

Figure 6.1 Influence of Sterics on Enantioselectivity



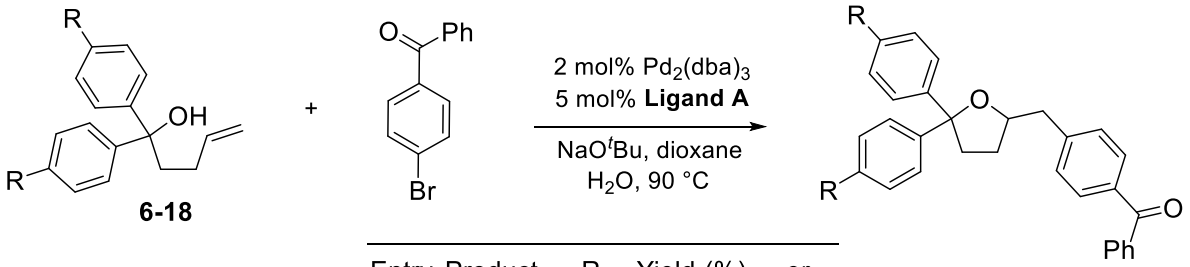
The influence of steric bulk on enantioselectivity prompted an additional study where geminal substitution was positioned on different carbons of the alken-ol (**Scheme 6.4**). Interestingly, no enantioselectivity was obtained for the synthesis of **6-15** where substitution occurs in the homoallyl position, but modest enantioselectivity was obtained for geminal methyl substitution in the allylic position as shown for the synthesis of **6-17**. It may be possible that increased steric bulk in the allylic position could enhance enantioselectivity, although this has yet to be evaluated.

Scheme 6.4 Investigation of Different Geminal Substitution Patterns



The effect of electronics on the phenyl ring was also studied, but before this study was conducted, a new challenge had to be overcome. While studying the effect of aryl ring electronics on the enantioselectivity approximately one year after initial publication, results were irreproducible. The use of new anhydrous dioxanes as solvent failed to reproduce previously achieved enantioselectivities. It was suspected that the older dioxanes solvent was contaminated with water. To test this hypothesis, the new bottle of anhydrous dioxanes was used as solvent with 2 equiv of water. These conditions restored previously obtained levels of enantioselectivity. These conditions were utilized to conduct the following study.

Table 6.1 Influence of Electronics on Enantioselectivity



Entry	Product	R	Yield (%)	er
1	**6-19**	OMe	61	92:8
2	**6-20**	Me	67	94:6
3	**6-13**	H	64	92:8
4	**6-21**	F	44	92:8
5	**6-22**	CF_3	82	89:11

The influence of electronics on the bulky aryl ring was tested by first synthesizing a variety of *p*- substituted alken-ols. The reactivity of each alken-ol was tested with 4-bromobenzophenone as shown in **Table 6.1**. In general, it seemed that electron-rich aryl rings improved enantioselectivity while electron-deficient aryl rings degraded the enantioselectivity, but a linear relationship could not be procured from this study.

6.3 Conclusion

This chapter describes the development of a new enantioselective synthesis of tetrahydrofurans via asymmetric Pd-catalyzed carboalkoxylation reactions. The development of new phosphite ligand **A** was crucial to achieving synthetically useful levels of enantioselectivity. While many electrophiles and many alken-ols were successfully utilized during the development of this reaction, several important details were unveiled that are essential to achieving high levels of enantioselectivity. Manipulations of the TADDOL backbone had relatively little influence on asymmetric

induction, but alterations to the chiral cyclohexanol portion of the ligand had a remarkable effect on enantioselectivity. Also, increased steric bulk next to the cyclizing alcohol improved the enantioselectivity. The studies herein will help guide future developments in the asymmetric construction of cyclic ethers.

In terms of future directions, the limitations associated with 1,2-disubstituted alkenes is a significant challenge that could be overcome. In order to expand the substrate scope of this reaction, this challenge should be addressed. As such, new ligands and new reaction conditions will have to be devised as the Wolfe group has witnessed previously the dramatic difference in reaction conditions required for obtaining the high diastereoselectivity by the Pd-catalyzed carboalkoxylation reaction of 1,2-disubstituted alkenes.

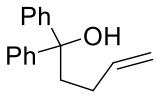
A portion of the work described in this chapter was published in *Angewandte Chemie* and *Angewandte Chemie International Edition*.[5]

6.4 Experimental Section

General: Reactions were carried out under nitrogen in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium was purchased from Strem Chemical Co. and used without further purification. Dichloromethane and toluene were purified using a GlassContour solvent system. Anhydrous dioxane was purchased from Acros Organics in a sure seal bottle and used as received. All other solvents and aryl halides were purchased from commercial sources and used as received. 1-(But-3-en-1-

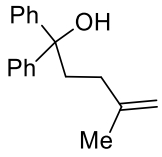
yl)cyclopentan-1-ol,[3c] and (+)-(1*S*,2*R*)-2-phenylcyclohexan-1-ol,[6] 4-methyl-2,2-diphenylpent-4-en-1-ol,[7] 3,3-dimethylpent-4-en-1-ol[8] and ligands[9] were synthesized according to literature procedures. 4-Penten-1-ol was purchased from commercial sources and was used without further purification. Yields refer to isolated compounds that are estimated to be $\geq$95% pure as judged by ^{1}H NMR or GC analysis unless stated otherwise. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Tables 2 and 3 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those in the manuscript.

Synthesis of Substrates:



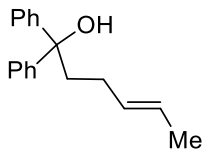
1,1-Diphenylpent-4-en-1-ol.[10] A flame dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with 4-pentenoyl chloride (5 mmol, 0.55 mL) and diethyl ether (50 mL). The mixture was cooled to 0 °C in an ice bath for five min and then PhMgBr (20 mL, 20 mmol, 1M in THF) was added dropwise to the flask. The resulting mixture was warmed to rt and stirred for 12 h, then the flask was cooled to 0 °C in an ice bath and slowly quenched with saturated aqueous ammonium chloride (10 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 25 mL. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel to afford the title compound (864 mg, 72%) as a colorless

oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 4 H), 7.33 (t, *J* = 8.1 Hz, 4 H), 7.24 (t, *J* = 6.6 Hz, 2 H), 6.85–6.78 (m, 2 H), 5.06–4.96 (m, 2 H), 2.44–2.38 (m, 2 H), 2.18 (s, 1 H), 2.12–2.04 (m, 2 H). Spectroscopic data was consistent with that previously reported in the literature.[10]

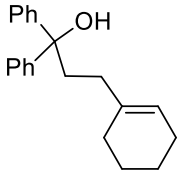


4-Methyl-1,1-diphenylpent-4-en-1-ol. A flame dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with PhMgBr (25 mL, 25 mmol, 1M in THF). The solution was cooled to 0 °C in an ice bath for five min. In a separate flask ethyl 4-methylpent-4-enoate[11] (1.0 g, 7 mmol) was dissolved in 20 mL anhydrous THF, and the resulting solution was added dropwise to the flask containing the cooled PhMgBr solution. The reaction mixture was then warmed to rt, stirred for 12 h, then was cooled to 0 °C in an ice bath and slowly quenched with saturated aqueous ammonium chloride (20 mL). The resulting mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethyl ether (3x25 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel to afford the title compound (1.54 g, 88%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.31, 0.98 Hz, 4 H), 7.34–7.31 (m, 4H), 7.25–7.20 (m, 2 H), 4.73 (s, 1 H), 4.70 (s, 1 H), 2.48–2.42 (m, 2 H), 2.25 (s, br, 1 H), 2.06–1.99 (m, 2 H), 1.74 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.1, 146.4, 128.4, 127.0, 126.2, 110.1, 78.5, 40.0, 32.2, 23.0; IR (film) 3469, 2932, 1446 cm^{-1}; MS

(EI) 252.1515 (252.1514 calcd for $C_{18}H_{20}O$, M +).



(*E*)-1,1-Diphenylhex-4-en-1-ol. The title compound was prepared from PhMgBr (50 mL, 50 mmol, 1M in THF) and (*E*)-ethyl hex-4-enoate[12] (2.28 g, 16.0 mmol) using a procedure analogous to that described above for the synthesis of **1e**. This procedure afforded the title compound (1.23 g, 30%) as a colorless solid, mp 53–54 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.43 (m, 4 H), 7.28–7.33 (m, 4 H), 7.20–7.24 (m, 2 H), 5.37–5.51 (m, 2 H), 2.33–2.38 (m, 2 H), 2.23 (s, 1 H), 1.96–2.03 (m, 2 H), 1.63 (dd, *J* = 5.9, 1.0 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.2, 131.3, 128.3, 127.0, 126.2, 125.7, 78.6, 41.7, 27.3, 18.1; IR (film) 3556, 2958, 1446 cm^{-1}; MS (EI) 252.1510 (252.1514 calcd for $C_{18}H_{20}O$, M +).

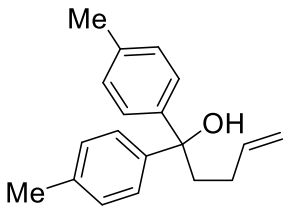


3-(Cyclohex-1-en-1-yl)-1,1-diphenylpropan-1-ol. The title compound was prepared from PhMgBr (11 mL, 11 mmol, 1M in THF) and 3-(cyclohex-1-en-1-yl)-1-phenylpropan-1-one[13] (1.2 g, 5.5 mmol) using a procedure analogous to that described above for the synthesis of **1e**. This procedure afforded the title compound (600 mg, 37%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.49 (m, 4 H), 7.28–7.34 (m, 4 H), 7.18–7.24 (m, 2 H), 5.41 (s, 1 H), 2.38–2.45 (m, 2 H), 2.37 (s, 1 H), 1.88–2.03 (m, 6 H),

1.48–1.67 (m, 4 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.2, 138.2, 128.3, 126.9, 126.2, 121.6, 78.7, 39.8, 32.5, 28.7, 25.4, 23.1, 22.7; IR (film) 3467, 2923, 1446 cm^{-1}; MS (EI) 292.1823 (292.1827 calcd for $C_{21}H_{24}O$, M +).

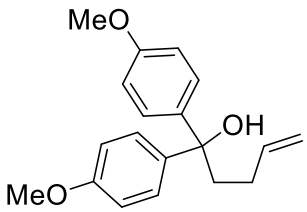
General Procedure 1 for Synthesis of Diphenyl Substituted Alken-ols

A flame dried 3-necked round bottom flask equipped with a stir bar and reflux condenser was cooled under a stream of nitrogen and charged with freshly ground magnesium (4 equiv) and anhydrous THF (1 mL THF/1 mmol Mg). Then, the aryl halide (3 equiv) was added as a solution in THF (0.2 mL / mmol aryl halide). The solution was cooled to 0 °C in an ice bath for five min. In a separate flask, ethyl pent-4-enoate (1 equiv) was dissolved in anhydrous THF (1 mL THF/ 1 mmol ester), and the resulting solution was added dropwise to the flask containing the cooled Grignard solution. The reaction mixture was then refluxed for 12 h, then was cooled to 0 °C in an ice bath, and slowly quenched with saturated aqueous ammonium chloride (2 mL / 1 mmol ester). The resulting mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethyl ether (3x25 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

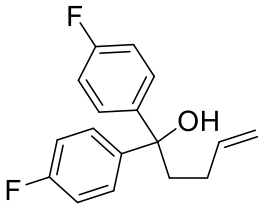


1,1-di-p-tolylpent-4-en-1-ol. The title compound was prepared from *p*-tolylmagnesium

bromide (46 mL, 30 mmol, 0.65 M in THF) and ethyl pent-4-enoate (1.3 g, 10.0 mmol) using General Procedure 1. This procedure afforded the title compound (2.2 g, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 4H), 5.84 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.95–4.90 (m, 1H), 2.36 – 2.27 (m, 9H), 2.05–1.99 (m, 2H).



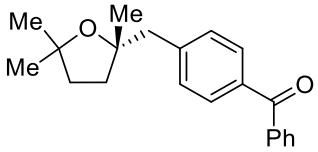
1,1-bis(4-methoxyphenyl)pent-4-en-1-ol. The title compound was prepared from (4-methoxyphenyl)magnesium bromide (46 mL, 30 mmol, 0.65 M in THF) and ethyl pent-4-enoate (1.3 g, 10.0 mmol) using General Procedure 1. This procedure afforded the title compound (1.8 g, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 4H), 6.87–6.81 (m, 4H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.00 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.94 (dq, *J* = 10.1, 1.4 Hz, 1H), 3.79 (s, 6H), 2.37–2.27 (m, 2H), 2.08–2.01 (m, 3H).



1,1-bis(4-fluorophenyl)pent-4-en-1-ol. The title compound was prepared from (4-fluorophenyl)magnesium bromide (46 mL, 30 mmol, 0.65 M in THF) and ethyl pent-4-enoate (1.3 g, 10.0 mmol) using General Procedure 1. This procedure afforded the title

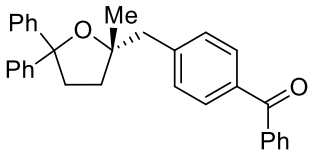
compound (2.1 g, 77%) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 4H), 7.03–6.97 (m, 4H), 5.84 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.04–4.94 (m, 2H), 2.37–2.31 (m, 2H), 2.14 (s, 1H), 2.07–2.00 (m, 2H).

General procedure 2 for asymmetric Pd-catalyzed carboalkoxylation reactions. A flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol %), **A** (5 mol %), the alcohol substrate (1.0 equiv), and NaO^{t}Bu (1.50–2.0 equiv). The flask was purged with N_2 then the aryl or alkenyl halide (1.40–2.0 equiv), and dioxane or toluene (0.10 M) was added. The resulting mixture was heated to 90 °C with stirring until the starting material had been consumed as judged by TLC analysis (ca. 12 h). The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6 mL/mmol substrate) was added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 x 5 mL) then the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.



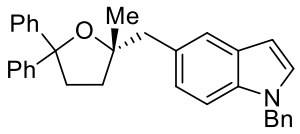
(+)-(*S*)-Phenyl{4-[(2,5,5-trimethyltetrahydrofuran-2-yl)methyl]phenyl}methanone (6-11). The general procedure was employed for the coupling of 2,5-dimethylhex-5-en-2-ol[1] (26 mg, 0.20 mmol) and 4-bromobenzophenone (94 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a

reaction temperature of 90 °C and a reaction time of 12 h in 2mL of dioxane. This procedure afforded the title compound (51.0 mg, 77%) as a colorless oil: $[\alpha]^{23}_{D}$ +3.48 (*c* 7.10, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.82 (m, 2 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 7.54–7.60 (m, 1 H), 7.47 (t, *J* = 10.0 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 2.85 (s, 2 H), 1.95–2.03 (m, 1 H), 1.76–1.85 (m, 2 H), 1.56–1.66 (m, 1 H), 1.25 (d, *J* = 2.9 Hz, 6 H), 1.14 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.8, 143.9, 138.1, 135.6, 132.3, 130.8, 130.1, 129.9, 128.4, 83.3, 81.7, 48.5, 38.6, 36.7, 29.9, 29.4, 28.6; IR (film) 2966, 1654, 1277 cm^{-1}; MS (ESI+) 309.1847 (309.1849 calcd for $C_{21}H_{24}O_2$, M + H^+). The enantiopurity was determined to be 38:62 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 2% IPA/Hexanes, 1.00 mL/min, λ 195 nm, RT= 10.1 and 10.8 min).



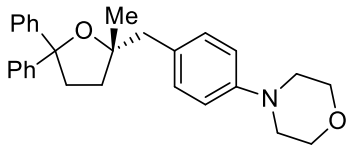
(+)-(*S*)-{4-[(2-Methyl-5,5-diphenyltetrahydrofuran-2 yl)methyl]phenyl}(phenyl)methanone (6-13). The general procedure was employed for the coupling of 4-methyl-1,1-diphenylpent-4-en-1-ol (51 mg, 0.20 mmol) and 4-bromobenzophenone (94 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C and a reaction time of 12 h in 2mL of dioxane. This procedure afforded the title compound (74.8 mg, 86%) as a colorless solid, mp 89–91 °C: $[\alpha]^{23}_{D}$ +20.9 (*c* 6.30, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.86 (m, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.58–7.64 (m, 1 H), 7.46–7.54 (m, 6 H), 7.26–7.40 (m, 6 H), 7.16–7.25 (m, 2 H), 3.03 (d, *J* = 13.2 Hz, 1 H), 2.91 (d, *J* = 13.2 Hz, 1 H), 2.62–2.75 (m, 2 H), 2.09 (m, 1 H), 1.86 (m 1 H), 1.31 (s, 3

H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.7, 148.2, 147.7, 143.8, 138.0, 135.6, 132.3, 130.6, 130.1, 129.9, 128.4, 128.1, 128.1, 126.7, 126.5, 126.0, 125.8, 88.7, 84.6, 48.5, 38.4, 37.4, 27.2; IR (film) 2966, 1654, 1277 cm^{-1}; MS (ESI+) 433.2160 (433.2162 calcd for $C_{31}H_{28}O_2$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 2% IPA/Hexanes, 1.00 mL/min, λ 275 nm, RT= 15.4 and 18.1 min).

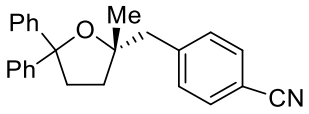


(+)-(*S*)-1-Benzyl-5-[(2-methyl-5,5-diphenyltetrahydrofuran-2-yl)methyl]-1H-indole (6-7). The general procedure was employed for the coupling of 4-methyl-1,1-diphenylpent-4-en-1-ol (51 mg, 0.20 mmol) and 1-benzyl-5-bromo-1*H*-indole (103 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (80.5 mg, 88%) as a colorless solid, mp 127–128 °C : $[\alpha]^{23}_D$ +22.6 (*c* 6.91, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43–7.51 (m, 5 H), 7.22–7.33 (m, 10 H), 7.10–7.20 (m, 5 H), 7.08 (d, *J* = 3.2 Hz, 1 H), 7.04 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.46 (d, *J* = 3.2 Hz, 1 H), 5.29 (s, 2 H), 3.04 (d, *J* = 13.4 Hz, 1 H), 2.90 (d, *J* = 13.4 Hz, 1 H), 2.62–2.66 (m, 2 H), 2.06–2.13 (m, 1 H), 1.67–1.75 (m, 1 H), 1.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 148.1, 137.8, 135.3, 129.8, 128.9, 128.7, 128.3, 128.1, 128.0, 127.7, 127.0, 126.5, 126.4, 126.2, 126.0, 124.8, 122.5, 109.1, 101.5, 88.4, 85.4, 50.2, 48.5, 38.8, 36.9, 27.1; IR (film) 2924, 1485, 1447 cm^{-1}; MS (ESI+) 458.2478 (458.2478 calcd for $C_{33}H_{31}NO$, M + H^+). The enantiopurity was determined to be 96:4 er

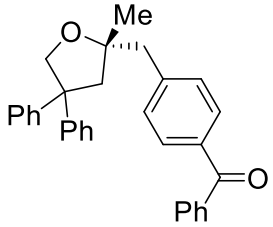
by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 11.6 and 30.3 min).



(+)-(*S*)-4-{4-[(2-Methyl-5,5-diphenyltetrahydrofuran-2-yl)methyl]phenyl}morpholine (6-5). The general procedure was employed for the coupling of 4-methyl-1,1-diphenylpent-4-en-1-ol (51 mg, 0.20 mmol) and 4-(4-bromophenyl)morpholine (87 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C and a reaction time of 12 h in 2 mL of dioxane. This procedure afforded the title compound (68.0 mg, 82%) as a colorless solid, mp 143–145 °C : $[\alpha]^{23}_D$ +28.8 (*c* 6.70, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 12.8, 7.5 Hz, 4 H), 7.22–7.33 (m, 4 H), 7.13–7.19 (m, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 3.87 (t, *J* = 4.7 Hz, 4 H), 3.09–3.14 (m, 4 H), 2.88 (d, *J* = 13.5 Hz, 1 H), 2.74 (d, *J* = 13.5 Hz, 1 H), 2.59–2.68 (m, 2 H), 1.98–2.03 (m, 1 H), 1.69–1.74 (m, 1 H), 1.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.4, 148.0, 131.3, 130.3, 128.1, 128.0, 126.5, 126.5, 126.1, 125.9, 115.4, 88.4, 85.1, 67.1, 49.7, 47.6, 38.7, 37.0, 27.0; IR (film) 2966, 1515, 1446 cm^{-1}; MS (ESI+) 414.2427 (414.2428 calcd for $C_{28}H_{31}NO_2$, M + H^+). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 2% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 8.7 and 10.7 min).

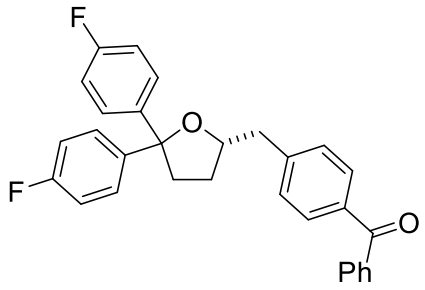


(+)-(*S*)-4-[(2-Methyl-5,5-diphenyltetrahydrofuran-2-yl)methyl]benzonitrile (6-6). The general procedure was employed for the coupling of 4-methyl-1,1-diphenylpent-4-en-1-ol (51 mg, 0.20 mmol) and 4-bromobenzonitrile (66 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C and a reaction time of 12 h in 2mL of dioxane. This procedure afforded the title compound (27.0 mg, 38%) as a colorless solid, mp 100–104 °C: $[\alpha]^{23}_D$ +23.9 (*c* 2.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2 H), 7.38–7.42 (m, 4 H), 7.27–7.30 (m, 4 H), 7.22–7.25 (m, 2 H), 7.13–7.22 (m, 2 H), 2.90–2.95 (d, *J* = 13.5 Hz, 1 H), 2.79–2.85 (d, *J* = 13.5 Hz, 1 H), 2.55–2.67 (m, 2 H), 1.96–2.02 (m, 1 H), 1.79–1.86 (m, 1 H), 1.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 147.4, 144.2, 131.7, 131.4, 128.2, 128.2, 126.8, 126.6, 126.0, 125.7, 119.4, 110.1, 88.8, 84.3, 48.5, 38.2, 37.5, 27.3; IR (film) 2925, 2223, 1607 cm^{-1}; MS (ESI+) 376.1670 (376.1670 calcd for $C_{25}H_{23}NO$, M + Na^+). The enantiopurity was determined to be 87:13 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 2% IPA/Hexanes, 1.00 mL/min, λ 195 nm, RT= 7.5 and 8.4 min).



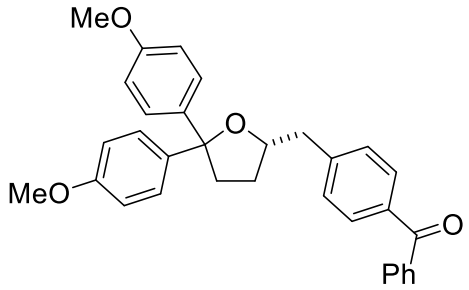
(+)-(*R*)-{4-[(2-Methyl-4,4-diphenyltetrahydrofuran-2-yl)methyl]phenyl}(phenyl)methanone (6-15). The general procedure was employed

for the coupling of 4-methyl-2,2-diphenylpent-4-en-1-ol[7] (51 mg, 0.20 mmol) and (4-bromophenyl)(phenyl)methanone (94 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C, and a reaction time of 12 h in 2mL of dioxane. This procedure afforded the title compound (73 mg, 84%) as a light yellow oil. $[\alpha]^{23}_D$= +0.01 (*c* 5.9, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.62 (m, 1 H), 7.46–7.52 (m, 2 H), 7.26–7.36 (m, 11 H), 7.16–7.22 (m, 2 H), 4.53 (d, *J* = 9.5 Hz, 1 H), 4.39 (d, *J* = 9.5 Hz, 1 H), 2.90 (d, *J* = 13.2 Hz, 1 H), 2.81 (d, *J* = 12.7 Hz, 1 H), 2.73 (d, *J* = 13.2 Hz, 1 H), 2.61 (d, *J* = 12.7 Hz, 1 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 146.5, 143.4, 138.0, 135.7, 132.4, 130.6, 130.1, 130.0, 128.6, 128.5, 128.4, 127.3, 126.4, 126.4, 83.7, 75.5, 56.5, 50.3, 47.8, 26.9; IR (film) 2926.7, 2247, 1654, 1276 cm^{-1}; MS (ESI+) 433.2164 (433.2162 calcd for $C_{31}H_{28}O_2$, M + H^+). The enantiopurity was determined to be 51:49 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 5% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 15.6 and 21.3 min).



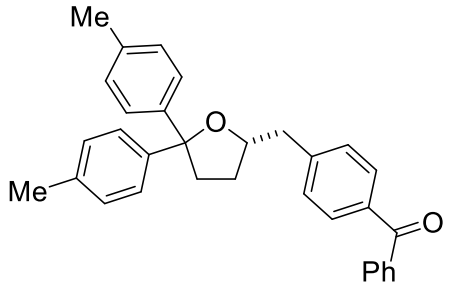
(S)-(4-((5,5-bis(4-fluorophenyl)tetrahydrofuran-2-yl)methyl)phenyl)(phenyl)methanone (6.21). The general procedure was employed for the coupling of 1,1-bis(4-fluorophenyl)pent-4-en-1-ol (55 mg, 0.20 mmol) and (4-bromophenyl)(phenyl)methanone (94 mg, 0.36 mmol) using a catalyst composed of

$Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C, and a reaction time of 12 h in 2mL of dioxane and 7 µL of water. This procedure afforded the title compound (40 mg, 44%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.61–7.56 (m, 1H), 7.49 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.39–7.32 (m, 6H), 6.97 (td, *J* = 8.7, 2.7 Hz, 4H), 4.40 (p, *J* = 6.6 Hz, 1H), 3.13 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.91 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.58 (dt, *J* = 12.4, 7.0 Hz, 1H), 2.44 (ddd, *J* = 12.4, 8.0, 6.8 Hz, 1H), 1.99 (dq, *J* = 12.2, 7.1 Hz, 1H), 1.77 (ddt, *J* = 12.6, 7.9, 6.7 Hz, 1H). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 4% IPA/Hexanes, 1.00 mL/min, λ 210 nm, RT= 15.4 and 17.2 min).

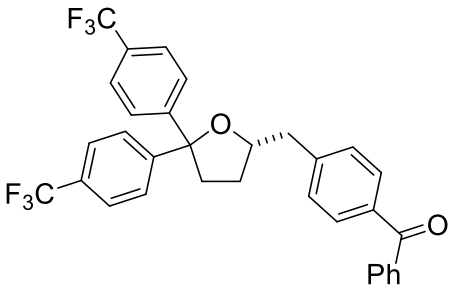


(S)-(4-((5,5-bis(4-methoxyphenyl)tetrahydrofuran-2-yl)methyl)phenyl)(phenyl)methanone (6-19). The general procedure was employed for the coupling of 1,1-bis(4-methoxyphenyl)pent-4-en-1-ol (60 mg, 0.20 mmol) and (4-bromophenyl)(phenyl)methanone (94 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C, and a reaction time of 12 h in 2mL of dioxane and 7 µL of water. This procedure afforded the title compound (58 mg, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.77 (m, 2H), 7.76–7.72 (m, 2H), 7.62–7.56 (m, 1H), 7.51–7.45 (m, 2H), 7.40–

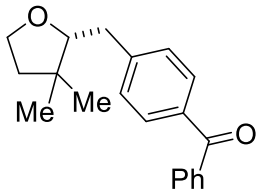
7.35 (m, 2H), 7.34–7.28 (m, 4H), 6.85–6.79 (m, 4H), 3.77 (d, *J* = 3.0 Hz, 6H), 3.15 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.89 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.57 (dt, *J* = 12.4, 7.0 Hz, 1H), 2.43 (dt, *J* = 12.4, 7.3 Hz, 1H), 2.03–1.91 (m, 1H), 1.76 (dq, *J* = 13.4, 6.9 Hz, 1H).The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 8% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 23.8 and 36.7 min).



(S)-(4-((5,5-di-p-tolyltetrahydrofuran-2-yl)methyl)phenyl)(phenyl)methanone (6-20). The general procedure was employed for the coupling of 1,1-di-p-tolylpent-4-en-1-ol (60 mg, 0.20 mmol) and (4-bromophenyl)(phenyl)methanone (94 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C, and a reaction time of 12 h in 2mL of dioxane and 7 µL of water. This procedure afforded the title compound (60 mg, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.76–7.73 (m, 2H), 7.61–7.57 (m, 1H), 7.49 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.34–7.28 (m, 4H), 7.09 (dd, *J* = 8.3, 2.4 Hz, 4H), 4.40 (p, *J* = 6.6 Hz, 1H), 3.16 (dd, *J* = 13.6, 6.5 Hz, 1H), 2.90 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.61 (dt, *J* = 12.2, 7.0 Hz, 1H), 2.47 (ddd, *J* = 12.3, 8.0, 6.7 Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 1.98 (dq, *J* = 12.1, 7.0 Hz, 1H), 1.82–1.72 (m, 1H). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 4% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 10.1 and 12.4 min).



(S)-(4-((5,5-bis(4-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methyl)phenyl)(phenyl)methanone (6-22). The general procedure was employed for the coupling of 1,1-bis(4-(trifluoromethyl)phenyl)pent-4-en-1-ol (75 mg, 0.20 mmol), (4-bromophenyl)(phenyl)methanone (94 mg, 0.36 mmol) using a catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C, and a reaction time of 12 h in 2mL of dioxane and 7 µL of water. This procedure afforded the title compound (91 mg, 82%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.74 (m, 4H), 7.62–7.52 (m, 9H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 4.43 (p, *J* = 6.6 Hz, 1H), 3.14 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.93 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.67 (dt, *J* = 12.4, 7.1 Hz, 1H), 2.58–2.49 (m, 1H), 2.03 (dq, *J* = 13.7, 6.9 Hz, 1H), 1.85–1.76 (m, 1H). The enantiopurity was determined to be 89:11 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 2% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 17.2 and 24.0 min).



(4-((3,3-dimethyltetrahydrofuran-2-yl)methyl)phenyl)(phenyl)methanone (6-17). The general procedure was employed for the coupling of 3,3-dimethylpent-4-en-1-ol (23 mg, 0.20 mmol) and (4-bromophenyl)(phenyl)methanone (94 mg, 0.36 mmol) using a

catalyst composed of $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and **A** (7.5 mg, 0.010 mmol), a reaction temperature of 90 °C, and a reaction time of 12 h in 2mL of dioxane and 7 µL of water. This procedure afforded the title compound (40 mg, 68%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2H), 7.77–7.74 (m, 2H), 7.58 (td, *J* = 7.3, 1.3 Hz, 1H), 7.50–7.45 (m, 2H), 7.40–7.36 (m, 2H), 3.92 (q, *J* = 8.2 Hz, 1H), 3.80 (td, *J* = 8.6, 4.6 Hz, 1H), 3.62 (dd, *J* = 9.0, 3.7 Hz, 1H), 2.82–2.69 (m, 2H), 1.86–1.73 (m, 2H), 1.08 (s, 3H), 1.04 (s, 3H). The enantiopurity was determined to be 63:37 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 2% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 18.4 and 20.2 min).

6.5 References

(1) (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504; (b) Bermejo, A.; Figadere, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep*. **2005**, *22*, 269; (c) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Alvarez, M. *Chem. Rev*. **2013,** *113*, 4567.

(2) For reviews on the synthesis of tetrahydrofurans, see: (a) Rainier, J.D. *Top. Heterocycl. Chem*. **2014**, *35*, 11; (b) Jalce, G.; Franck, X.; Figadere, B. *Tetrahedron:Asymmetry*, **2009**, *20*, 2537; (c) Wolfe, J.P.; Hay, M.B. *Tetrahedron* **2007**, *63*, 261; (d) Muzart, J. *Tetrahedron*, **2005**, *61*, 5955; (e) Harmange, J.C.; Figadere, B. *Tetrahedron: Asymmetry,* **1993**, *4,* 1711.

(3) (a) Wolfe, J.P.; Rossi, M.A. *J. Am. Chem. Soc*. **2004**, *126*, 1620; (b) Hay, M.B.; Wolfe, J.P. *J. Am. Chem. Soc*. **2005**, *127*, 16468; (c) Hay, M.B.; Hardin, A.R.;

Wolfe, J.P. *J. Org. Chem*. **2005**, *70*, 3099; (d) Ward, A.F.; Wolfe, J.P. *Org. Lett*. **2009**, *11*, 2209; (e) Ward, A.F.; Wolfe, J.P. *Org. Lett*. **2010**, *12*, 1268.

(4) Hopkins, B.A. Enantioselective Synthesis of Heterocycles Via Palladium Catalyzed Alkene Difunctionalization Reactions. Ph. D. Thesis, University of Michigan, Ann Arbor, MI, **2015.**

(5) (a) Hopkins, B.A.; Garlets, Z.J.; Wolfe, J.P. *Angew. Chem*. **2015**, *127*, 13588; (b) Hopkins, B.A.; Garlets, Z.J.; Wolfe, J.P. *Angew. Chem. Int. Ed*. **2015**, *54*, 13390.

(6) Carpenter, B.E.; Hunt, I.R. Keay, B.A. *Tetrahedron: Asymmetry* **1996**, *7*, 3107.

(7) Jeong, Y.; Kim, D. -Y.; Choi, Y.; Ryu, J. -S. *Org. Biomol. Chem*, **2011**, *9*, 374.

(8) Srikrishna, A.; Dethe, D.H.; Kumar, R.P. *Tetrahedron Letters*, **2004**, *45*, 2939.

(9) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.-M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011.

(10) Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* **2010**, *75*, 5008.

(11) Cai, Z.; Yongpruksa, N.; Harmata, M. *Org. Lett.* **2012**, *14*, 1661.

(12) Hay, M.B.; Wolfe, J.P. *J. Am. Chem. Soc.* **2005**, ***127***, 16468.

(13) Faulkner, A.; Scott, J.S.; Bower, J.F. *Chem. Comm.* **2013**, *49*, 1521.